

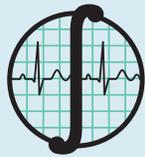


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**Dr. César A. González Díaz**  
EDITOR EN JEFE 2020-2021

## CARTA DEL EDITOR

### Estimados lectores:

La *Revista Mexicana de Ingeniería Biomédica* (The Mexican Journal of Biomedical Engineering), órgano oficial de divulgación de la Sociedad Mexicana de Ingeniería Biomédica, se ha consolidado como una de las mejores revistas científica de su campo en América Latina, tal logro es el resultado de 41 años de un esfuerzo continuo de muchas personas.

Mi nombre es César Antonio González Díaz y tengo el honor de fungir como actual editor en jefe (2020-2021). Me desempeño como profesor e investigador en el Instituto Politécnico Nacional-México, y cuento con 15 años de experiencia en la publicación y revisión de artí-

culos científicos originales. Considero que liderar el actual comité editorial de nuestra revista, es una responsabilidad y también una oportunidad para contribuir en el fortalecimiento de nuestra comunidad de Ingeniería Biomédica.

Dentro de los objetivos relevantes que me he propuesto como actual editor en jefe, son el de incrementar la visibilidad internacional de nuestra revista, así como su índice de citas y factor de impacto. Para tal efecto, la estrategia que hemos diseñado consiste en dos aproximaciones fundamentales: 1) la integración de un sólido y reconocido comité científico editorial y asistentes editoriales, y 2) la publicación exclusiva en el idioma inglés. El equipo que hemos integrado nos hemos comprometido a velar por mantener un contenido editorial con calidad académica y rigurosidad científica.

Los exhortamos a unirse a nuestro esfuerzo, y lograr con nosotros el engrandecimiento de nuestra revista, el envío de sus reportes científicos de investigaciones originales, revisiones, notas técnicas o cartas al editor sin duda contribuirán en el logro de los objetivos planteados.

Por último, quiero reconocer y agradecer la confianza que me ha brindado la actual mesa directiva de la Sociedad Mexicana de Ingeniería Biomédica para dirigir el rumbo de nuestra revista, estoy seguro de que cumpliremos con sus expectativas. Gracias.

*Dr. César A. González Díaz*

## EDITOR'S LETTER

### Dear Readers:

Greetings from the *Mexican Journal of Biomedical Engineering* (MJBE) (Revista Mexicana de Ingeniería Biomédica), official organ of the Mexican Society of Biomedical Engineering (Sociedad Mexicana de Ingeniería Biomédica). The journal has become the best scientific journal in its field in Latin America. This achievement is the result of 41 years of continuous effort of a large number of people.

I, César Antonio González Díaz, have the honor of acting as the current editor-in-chief of the journal for the next two years. I am a professor/researcher of the Instituto Politécnico Nacional in Mexico City, Mexico, and have been publishing original scientific articles for over 15 years. The position of editor-in-chief is a great responsibility and at the same time an opportunity to contribute to the strengthening of our community of biomedical engineers.

Among the most important objectives that I have set for the journal in the near future is to increase its international visibility and impact factor. To meet these goals, the editorial staff has established two relevant policies: 1) the integration of a well-recognized group of researchers as an editorial committee to review the scientific manuscripts that are sent to the journal, and 2) the decision to publish articles exclusively in English. The newly formed committee has committed itself to strict standards of academic quality and scientific rigor.

The editorial committee exhorts all researchers in the field to join the effort in making the MJBE an internationally recognized journal. We ask that you send manuscripts related to biomedical engineering in order to be published in our regular or special issues, whether they be original research, review papers, short communications or letters to the editor.

Finally, I would like to express my gratitude to the Board of Directors of the Mexican Society of Biomedical Engineering for trusting in me to lead the course of the journal for the next two years. I am sure that we will meet our goals.

**Prof. César A González Díaz**

EDITOR-IN-CHIEF 2020-2021

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## Desarrollo y Simulación de un Algoritmo de Control Automatizado para Insulinoterapia de Urgencias Hiperglucémicas en Diabetes

### Development and Simulation of an Automated Control Algorithm for Insulin Therapy of Hyperglycemic Emergencies in Diabetes

*J. Becerril-Rico*

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#### RESUMEN

El presente trabajo describe el desarrollo y simulación de un algoritmo para el control automático de la infusión de insulina en el manejo glucémico de pacientes con cetoacidosis diabética (CAD) y estado hiperosmolar hiperglucémico (EHH). Se programó un algoritmo que calcula la insulina necesaria para lograr un descenso glucémico de 50 mg/dL/h hasta llegar a glucemias de 250 mg/dL, para posteriormente mantenerlas en 220 mg/dL hasta la remisión de la patología. La simulación del software se realizó haciendo uso de registros glucémicos de 10 pacientes con CAD manejados en el Hospital Juárez de México. Los resultados de la simulación mostraron una incidencia 6 veces menor de hipoglucemias, así como un 33.7% menos de insulina necesaria dentro del tratamiento, sin diferencias entre los descensos medios de glucosa por hora de las mediciones reales y simuladas. Este software propone un uso innovador de los llamados páncreas artificiales al aplicarlos en urgencias hiperglucémicas, implementando además el uso de la sensibilidad a la insulina como variable para el funcionamiento de los mismos. Los resultados demuestran que el algoritmo podría ser capaz de lograr un manejo glucémico apegado a las guías de tratamiento, generando un menor gasto de insulina y evitando hipoglucemias durante la terapéutica, con una posible aplicación en dispositivos biomédicos autónomos.

**PALABRAS CLAVE:** Sistema de infusión de insulina; control de glucosa en lazo cerrado; complicación diabética; cetoacidosis diabética; páncreas artificial.

### ABSTRACT

This paper describes the development and simulation of an algorithm for the automatic control of insulin infusion, in the glycemic management of patients with diabetic ketoacidosis (CAD) and hyperglycemic hyperosmolar state (EHH). An algorithm was programmed to calculate the requirement insulin for a glycemic decrease of 50 mg/dL/h until reach 250 mg/dL in blood glucose levels, and thus maintaining it at 220 mg/dL until the pathology remission. The software simulation was performed using glycemic records of 10 patients with CAD managed in the Hospital Juárez de México. The results of the simulation showed a lower incidence of hypoglycemia, as well as a lower insulin requirement within the treatment, without differences in the average glucose decreases per hour between real and simulated measurements. This software proposes an innovative use of the artificial pancreas in hyperglycemic emergencies, and also implementing the use of insulin sensitivity as a variable for their function. The results show that the algorithm could be able to achieve glycemic management attached to the treatment guidelines, generating lower insulin expenditure and avoiding hypoglycemia during therapy, with a possible application in autonomous biomedical devices.

**KEYWORDS:** Insulin infusion system; closed-loop glucose control; diabetes complications; diabetic ketoacidosis; artificial pancreas.

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## INTRODUCCIÓN

La cetoacidosis diabética y el estado hiperosmolar hiperglicémico son complicaciones agudas de la diabetes que se caracterizan por ser claras emergencias hiperglucémicas que ponen riesgo la vida de los pacientes <sup>[1]</sup>. Su manejo amerita un control glucémico estrecho debido a las posibles complicaciones que pueden generar <sup>[2]</sup>, lo que involucra una alta demanda de tiempo del personal de salud, un aspecto difícil de cumplir en centros hospitalarios de alta demanda y alta saturación. El objetivo de este trabajo es describir el diseño y simulación de un software para el control automatizado, tipo Proporcional Integral Derivativo (PID) para el manejo de pacientes con cetoacidosis diabética (CAD) o estado hiperosmolar hiperglucémico (EHH) en el servicio de urgencias. El sistema descrito basa su funcionamiento en los conocidos páncreas artificiales, sin embargo, su utilización busca el descenso controlado de la glucosa sérica en un servicio de urgencias médicas con la finalidad de evitar complicaciones en el manejo, como son la hipoglucemia, edema cerebral y deshidratación, además de buscar un posible mejoramiento en los resultados terapéuticos tras su utilización dentro de bombas de infusión autónomas.

### Generalidades: CAD y EHH

A pesar de los avances en el manejo de la diabetes mellitus, la CAD y el EHH son aún causas importantes de morbilidad y mortalidad. La incidencia anual de la CAD se estima en 4 - 8 episodios por cada 1,000 pacientes diabéticos <sup>[2]</sup>. La incidencia de EHH es menor que la de CAD, siendo causa de menos del 1% de las admisiones en pacientes diabéticos, sin embargo, tiene mayores tasas de mortalidad <sup>[2]</sup>.

La CAD se caracteriza por datos bioquímicos de hiperglucemia, cetonemia, y acidosis con anión gap elevado. Por su parte el EHH se caracteriza por hiperglucemia, grados mínimos y variables de cetonemia, existencia de hiperosmolaridad sérica, un mayor grado de deshidratación, y por lo general ausencia de acide-

mia <sup>[1]</sup>. Otra diferencia entre estas dos patologías es que el EHH afecta con mayor frecuencia a pacientes con diabetes tipo 2, mientras que la CAD se relaciona con diabetes tipo 1, sin embargo, dentro de la población mexicana existe mayor prevalencia de CAD asociada a diabetes tipo 2 <sup>[2] [3] [4]</sup>.

Dentro de la CAD se genera una total deficiencia de insulina sérica, lo que desencadena un estado catabólico caracterizado por glucogenólisis, proteólisis, y lipólisis, permitiendo esto último la utilización de ácidos grasos para la síntesis de cuerpos cetónicos en el tejido hepático, que pueden ser utilizados como sustratos energéticos por algunos tejidos, sin embargo, resulta también en cetonemia con la consecuente disminución del pH sérico <sup>[5]</sup>. En el EHH hay una insulopenia no tan extrema como en la CAD, lo que evita la generación de lipólisis y cetogénesis <sup>[5]</sup>.

Estos eventos fisiopatológicos se generan tras algún factor precipitante, como lo puede ser una terapia inadecuada de insulina, infecciones, un evento vascular cerebral u otros eventos isquémicos de corazón o pulmón, pancreatitis, abuso de alcohol o drogas y el consumo de ciertos medicamentos, como corticoesteroides, tiazidas, diuréticos, simpaticomiméticos y antipsicóticos <sup>[6]</sup>.

En cuanto a la presentación clínica de la CAD y el EHH, se basa en poliuria, polifagia, polidipsia, debilidad, y signos físicos de deshidratación. La respiración de Kussmaul, náuseas, vómito, dolor abdominal, y aliento a manzana, se relacionan más a CAD <sup>[7]</sup>. La presencia de alteraciones en el estado de alerta, que van desde la somnolencia hasta el coma, son más usuales en el EHH <sup>[7]</sup>.

El manejo de dichas entidades clínicas consiste en primera instancia en la reposición de fluidos utilizando solución de cloruro de sodio (NaCl) al 0.9%, a una velocidad de 15 - 20 ml/kg/h en la primera hora,

según la ADA (American Diabetes Association) [8]. En las siguientes horas es posible continuar el manejo con NaCl 0.9% o NaCl 0.45%, según sean los niveles séricos de sodio; ambas opciones se dan a 250 - 500 ml/h + 20 - 30 mEq/L de cloruro de potasio [5].

Los niveles séricos de potasio deben evaluarse antes de iniciar la insulino terapia, ya que si estos son menores a 3.3 mEq/L se debe de reponer potasio antes de iniciar con la administración de insulina. En caso de tener niveles mayores a 5.2 mEq/L se recomienda no añadir potasio en las soluciones intravenosas. Si los niveles de potasio se encuentran en 3.3 - 5.2 mEq/L se recomienda añadir 20 - 30 mEq de cloruro de potasio (KCl) por cada litro de solución intravenosa (IV) infundida, procediendo a la insulino terapia [5].

El tratamiento con insulina se inicia con un bolo de 0.1 UI/kg, seguido a los 5 minutos por una infusión continua de 0.1 UI/kg/h; alternativamente puede omitirse el bolo de insulina e iniciar con la infusión continua de 0.14 UI/kg/h. Si los niveles de glucosa no disminuyen en 50 - 70 mg/dL en la primera hora, se debe duplicar la dosis de infusión cada hora hasta alcanzar esta meta [5].

Al alcanzarse glucemias de 200 mg/dL en CAD y 250 - 300 mg/dL en EHH, se cambian las soluciones a solución glucosada al 5% (SG5%) + NaCl 0.45% a una velocidad de 150 - 250 ml/h, manteniendo una infusión de insulina de 0.02 - 0.05 UI/kg/h, siempre evitando valores de glucosa sérica menores a 200 mg/dL en CAD y 250 - 300 mg/dL en EHH, para evitar causar edema cerebral [5] [8].

Una vez alcanzados los criterios de resolución para CAD y EHH se suspende la insulina IV y se continúa con insulina subcutánea en dosis 0.5 - 0.8 UI/kg/día [2]. Los criterios de resolución para CAD incluyen glucosa < 200 mg/dL y dos de los siguientes:  $\text{HCO}_3^- \geq 15$  mEq/L,  $\text{pH} > 7.3$ , y anión GAP  $\leq 12$  mEq/L [1] [2].

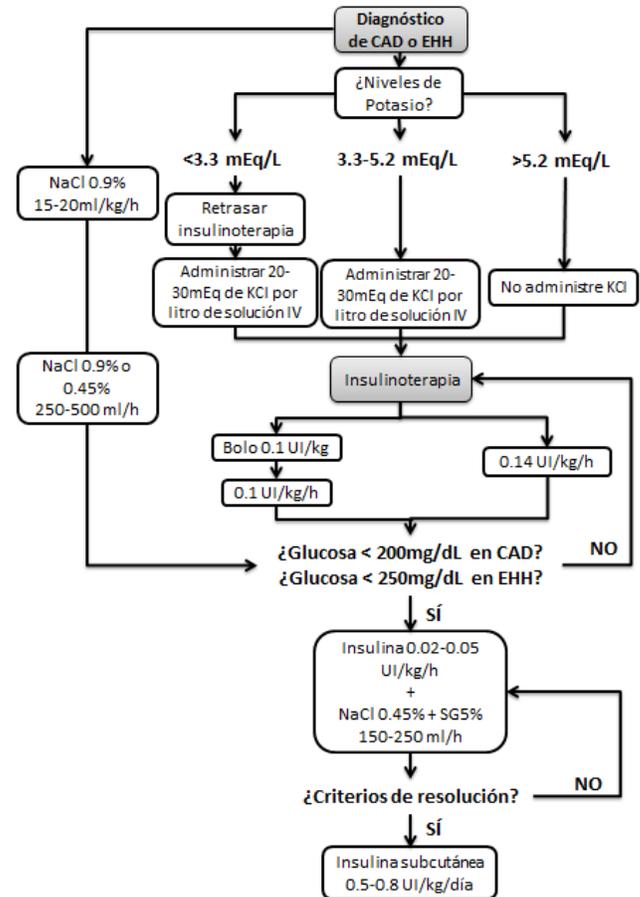


FIGURA 1. Algoritmo de tratamiento para CAD y EHH [2] [3] [6].

En cuanto a los criterios de resolución para EHH, son osmolaridad sérica < 320 mOsm/kg y la recuperación del estado de alerta [1] [2].

Entre las principales complicaciones del manejo de CAD y EHH se encuentran desequilibrios electrolíticos, principalmente de potasio, así como edema cerebral (0.3 - 1%) e hipoglucemia [9].

## Sistemas PID y páncreas artificial

El objetivo de un sistema de control es regular las señales de salida de un sistema con base en respuestas o modificación de variables de operación, con el fin de mantener la o las variables objetivo dentro de parámetros preestablecidos, esto a pesar de perturbaciones que pudieran afectar el sistema [10]. En las últimas décadas, se ha buscado la aplicación de estos sistemas

para el control de pacientes diabéticos, con la intención de mantener un control más estricto en los niveles de glucosa sérica, similar a como se haría de manera fisiológica. Estos equipos han sido llamados páncreas artificiales, los cuales sensan continuamente los niveles glucémicos del paciente y generan una respuesta de liberación de insulina, basados en el valor de referencia de glucosa y la señal de error del controlador, siendo común el uso de sistemas tipo PID para esta tarea <sup>[11]</sup> <sup>[12]</sup>.

Como ejemplo de la aplicación de sistemas de control PID en el manejo glucémico se encuentra el trabajo de Steil <sup>[13]</sup>, donde se evalúa un sistema PID de lazo cerrado con monitoreo glucémico y liberación de insulina vía subcutánea, comparándolo con el uso de una bomba de infusión de insulina de lazo abierto, en el manejo de pacientes con diabetes mellitus tipo 1. En este trabajo se observó una incidencia de hipoglucemias similar entre ambos manejos, sin embargo, con el uso del sistema PID no se observaron hiperglucemias severas <sup>[13]</sup>. Otro trabajo que ejemplifica esta aplicación es el presentado por Huyett, el cual propone un sistema implantable con operación a nivel intraperitoneal con un funcionamiento que incluye un sistema PID, modelo de control predictivo y lógica fuzzy <sup>[14]</sup>.

Dentro de los sistemas de lazo cerrado para el control glucémico, el algoritmo de control resulta una de las partes más importantes y complicadas de desarrollar, pero que marca la manera en cómo funcionará el sistema, sus ventajas y desventajas. En estos sistemas, es común el uso de algoritmos de control tipo PID, principalmente debido a su robustez y fácil desarrollo <sup>[15]</sup>. En el trabajo de Hu y Li, por ejemplo, se muestra el desarrollo y simulación de un algoritmo de control PID que basa su funcionamiento en la estimación del tiempo de acción de la insulina (IOB), un punto que resulta innovador. Estos autores establecen el IOB como un factor que varía de forma interpersonal e intrapersonal debido a múltiples factores, cuyo cálculo y uso dentro

del algoritmo PID permite mejorar los resultados y evitar hipoglucemias <sup>[15]</sup>. El uso del IOB permite al algoritmo tomar en cuenta el estado metabólico actual del paciente para generar la señal de salida del sistema, un punto poco considerado por muchos de estos sistemas para insulinoterapia, pero de gran importancia en estados patológicos como CAD y EHH.

A pesar de que los algoritmos tipo PID son los más utilizados en sistemas automatizados de insulinoterapia, no son los únicos, existen los que emplean modelos de control predictivo (MPC), control adaptativo, control en modo deslizante, etc. En el trabajo de Pinsky *et al*, por ejemplo, se compara el uso de un algoritmo de control PID con uno MPC en el control glucémico de pacientes con diabetes tipo 1. Dentro del mismo se observó que el algoritmo MPC logró mantener a los pacientes en rangos glucémicos meta durante mayor tiempo que el algoritmo PID, además de lograr cifras glucémicas menores 5 h posteriores a la ingesta de alimentos. Sin embargo, no se encontraron diferencias estadísticas en el tiempo que tardaron ambos algoritmos para llevar a los pacientes a cifras glucémicas meta posterior a la ingesta de alimentos, lo que deja ver que ambos responden de manera similar ante cambios glucémicos bruscos <sup>[16]</sup>.

A pesar de la existencia de diversos dispositivos de este tipo para el manejo glucémico de pacientes con diabetes mellitus, no existe en la literatura ningún trabajo que enfoque tales dispositivos al manejo de urgencias hiperglucémicas en este grupo de pacientes. Como se ha mencionado, las características intrínsecas de la CAD y el EHH vuelven todo un reto el control glucémico de estos pacientes, dado principalmente por las fuertes variaciones en la sensibilidad a la insulina, liberaciones incrementadas y variables de glucosa en el hígado, así como por los mismos desequilibrios fisiológicos generados por el propio manejo, como es el caso de la rehidratación hídrica agresiva y otros medicamentos que generan variaciones en el volumen

intravascular. Esta dificultad en el control glucémico genera una gran demanda de tiempo para el personal en los servicios de urgencias médicas, por lo que la automatización de esta tarea podría resultar en una disminución de tiempo, costos y personal requerido para el manejo de pacientes con CAD y EHH.

En párrafos anteriores se ha mostrado que la utilización de sistemas de lazo cerrado con liberación automatizada de insulina podría resultar en mejores resultados terapéuticos en pacientes diabéticos, por lo que siguiendo esta premisa, el presente trabajo busca ampliar las aplicaciones y beneficios de estos dispositivos al área de las complicaciones agudas de la diabetes mellitus. Como primer paso en el desarrollo de un sistema de lazo cerrado con liberación automatizada de insulina para el manejo de CAD y EHH, se presenta el desarrollo y simulación de un algoritmo de control automatizado tipo PID, que fija las bases teóricas para el funcionamiento de este tipo de sistema. Por otra parte, se mencionó que el uso de variables como IOB mejora el funcionamiento de sistemas PID para el control glucémico, por lo que el algoritmo aquí planteado intenta retomar esta idea utilizando la sensibilidad a la insulina como método indirecto en la evaluación del estado metabólico altamente cambiante de pacientes con CAD y EHH.

## METODOLOGÍA

Se contempló un controlador automatizado tipo PID con retroalimentaciones de glucosa cada hora, que pudiera establecer la insulina necesaria para el manejo de paciente con CAD y EHH. La decisión de un sistema PID se basó en su robustez, adaptabilidad, fácil implementación y gran capacidad para compensar errores previos, actuales, así como predecir errores futuros, características de relevancia para el control de señales con alta variabilidad, como son los cambios glucémicos en pacientes con CAD y EHH <sup>[17]</sup>. El sistema se diseñó como software tipo aplicación (Figura 3), para mayor facilidad en el uso por parte del personal

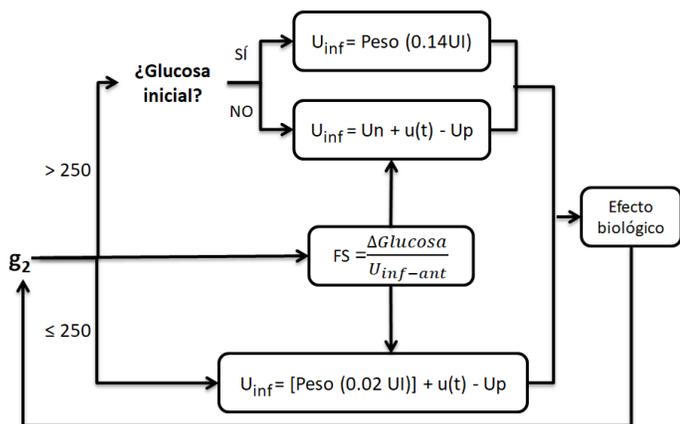
médico, bajo costo para su aplicación clínica, y pensando en una posterior fase de prueba, antes de una posible implementación como dispositivo biomédico autónomo con monitoreo glucémico continuo vía intravenosa o subcutánea.

El controlador del sistema tendrá como señal de entrada, a través de cajas de texto en el software, los niveles de glucosa capilar ingresados cada hora (tiempo de muestreo del sistema) y el peso del paciente. Como señal de salida, se contempla las unidades de insulina (UI) a infundir durante la siguiente hora de tratamiento. Con esta señal de salida se busca cumplir como metas de tratamiento un descenso de la glucosa capilar de 50 mg/dL/hora hasta llegar a valores de 250 mg/dL, a partir de lo cual se buscará mantener los niveles de glucosa en 220 mg/dL con oscilaciones esperadas entre 200 - 250 mg/dL, que se llamarán hipoglucemias e hiperglucemias, respectivamente. Se eligió como valor de referencia 220 mg/dL, ya que es un punto entre lo recomendado para CAD (mayor de 200 mg/dL) y EHH (250 mg/dL) <sup>[6]</sup>, además de ser un valor de referencia seguro ante posibles compensaciones excesivas del sistema que pudieran desencadenar hipoglucemias.

Según lo expuesto en el párrafo anterior, el funcionamiento del controlador se divide en 2 fases: el funcionamiento cuando existen niveles de glucosa capilar mayores a 250 mg/dL, y el funcionamiento del mismo con glucosas menores a 250 mg/dL. La Figura 2 muestra el algoritmo de decisiones del software para ambas fases.

### Funcionamiento del sistema con glucosa > 250 mg/dL

Cuando las glucosas ingresadas al programa son mayores a 250 mg/dL se calculará la infusión de insulina con la finalidad de reducir la glucemia en 50 mg/dL/hora, como se recomienda en las guías de tratamiento <sup>[17]</sup>. El cálculo de la insulina a infundir se realizó tomando en cuenta: 1) la sensibilidad a la insulina



**FIGURA 2. Algoritmo de decisiones del sistema.**

$g_2$ : glucosa actual,  $U_{inf}$ : insulina total a infundir en la siguiente hora,  $U_p$ : insulina activa de lo infundido en la hora anterior,  $U_n$ : insulina necesaria para bajar glucosa 50 mg/dL en la siguiente hora, FS: sensibilidad a la insulina.

del paciente en el momento actual, 2) la insulina necesaria para bajar la glucosa capilar 50 mg/dL/hora, 3) la insulina calculada por el sistema PID para corregir el error en el descenso de la glucosa capilar, 4) la insulina circulante con potencial actividad farmacológica dentro del cuerpo del paciente.

Como se mencionó, la sensibilidad a la insulina (FS) es un reflejo del estado metabólico del paciente en un momento dado, multifactorial, y altamente variable a lo largo del tratamiento de CAD y EHH. Para saber la insulina que necesita el paciente es necesario conocer antes la sensibilidad a la insulina, sin embargo, solo es posible saber el nivel de sensibilidad a la insulina observando la respuesta que tiene el paciente ante la administración de la misma. Según esto, no es posible saber la sensibilidad a la insulina sin antes infundirla al paciente, por lo que la primera acción del programa consiste en solicitar la glucosa inicial del paciente y su peso, para recomendar la infusión de insulina en dosis de 0.14 UI/kg durante la siguiente hora, según lo recomendado por las guías de tratamiento [7]. Tras dicha infusión, el programa espera reducir la glucosa en 50 mg/dL para la siguiente hora [18].

Una vez transcurrida la primera hora de tratamiento, el software obtiene la sensibilidad a la insulina del paciente conforme a la siguiente ecuación [19]:

$$FS = \frac{\Delta Glucosa \left(\frac{mg}{dL}\right)}{Insulina\ usada\ en\ la\ hora\ anterior(UI)} \quad (1)$$

Después de transcurrir la primera hora, y sabiendo la sensibilidad a la insulina que tiene el paciente, el software calcula la insulina necesaria para bajar 50 mg/dL ( $U_n$ ) en la segunda hora de tratamiento, contemplando la glucosa actual ( $g_2$ ) y el valor de referencia para la siguiente hora

$$\left(g_2 - \frac{50mg}{dL}\right),$$

haciendo uso de la ecuación que señalamos a continuación, la cual se deriva a su vez de la ecuación 1 al despejarla para la insulina y proyectarla hacia la próxima hora:

$$U_n = \frac{g_2 - (g_2 - 50\ mg/dL)}{FS} \quad (2)$$

El siguiente paso sería calcular la insulina necesaria para compensar el error de descenso en la glucosa, la cual denotaremos como  $u(t)$ , cuyo cálculo se basa en la siguiente ecuación general [10]:

$$u(t) = K_p e(t) + \frac{K_p}{T_i} \int_0^t e(t) dt + K_p T_D \frac{d e(t)}{dt} \quad (3)$$

Donde  $e(t)$  hace referencia al error en el descenso de la glucosa que se tuvo durante la hora anterior. Para explicar matemáticamente esto, tomaremos a ( $g_1$ ) como la glucosa obtenida en la hora anterior. Por ello,  $e(t)$  podría definirse como:

$$e(t) = g_2 - \left(g_1 - 50 \frac{mg}{dL}\right) \quad (4)$$

Las constantes para la ecuación 3 se establecerán como un tiempo derivativo ( $TD$ ) de 90 min, y un tiempo integral ( $TI$ ) de 150 min. Estos valores se derivan de simulaciones del algoritmo realizadas con valores prueba de  $TD$  entre 60 - 90 min, y de  $TI$  entre 150 - 450 min, valores utilizados por Steil <sup>[20]</sup>, encontrándose que con  $TD = 90$  min y  $TI = 150$  min: se obtuvieron resultados menores en el  $e(t)$ , así como menor frecuencia de hipoglucemias y descensos de glucosa por hora mayores a 100 mg/dL. La constante proporcional ( $K_p$ ) se estableció como una variable dependiente de  $TD$  y la sensibilidad a la insulina según la siguiente ecuación <sup>[13]</sup>:

$$K_p = \frac{1}{(TD)(FS)} \quad (5)$$

Con los valores de  $U_n$  y  $u(t)$  se tiene la insulina que necesitará el paciente para la siguiente hora, lo cual se denotará como insulina subtotal ( $U_{sbt}$ ).

$$U_{sbt} = U_n + u(t) \quad (6)$$

No obstante, a esta cifra es necesario restarle aquella insulina que fue infundida la hora anterior y que todavía permanece activa en el cuerpo del paciente. Ello depende de la tasa de degradación de la insulina. Para el presente trabajo fue planteado un sistema unicompartmental intravascular, donde se considera que la tasa de degradación de la insulina es de 0.18 UI/min, es decir, 10.8 UI/hora <sup>[21] [22] [23]</sup>. Por ende, para poder determinar la cantidad de insulina que permanece activa de lo infundido en la hora anterior ( $U_p$ ), se deberá restar 10.8 unidades a la insulina infundida durante la hora anterior ( $U_{n-1}$ ):

$$U_p = U_{n-1} - 10.8 UI \quad (7)$$

Finalmente la insulina total a infundir durante la siguiente hora ( $U_{inf}$ ), es decir, la señal de salida del controlador sería:

$$U_{inf} = U_n + u(t) - U_p \quad (8)$$

Este proceso se repite cada hora para el cálculo de la insulina a infundir en la hora siguiente.

Como medida de seguridad se limitó a  $U_{inf}$  para valores máximos de  $\pm 15$  unidades para pacientes con peso 50 - 90 kg,  $\pm 12$  unidades con peso < 50 kg, y  $\pm 18$  con peso > 90 kg. Tal decisión se tomó basada en simulaciones anteriores que mostraban la generación de fuertes descensos de glucosa/hora, por lo que esta adecuación al algoritmo busca limitar la intensidad en el descenso de la glucosa, así como el riesgo de hipoglucemia e hiperglucemias.

### Funcionamiento del sistema con glucosa < 250 mg/dL

Una vez que se han alcanzado niveles de glucosa capilar menores a 250 mg/dL, o si la glucosa inicial del paciente era menor a esa cifra, el software cambia el valor de referencia de glucosa al cual quiere llegar, estableciéndolo en 220 mg/dL. En este punto, el software funciona de manera similar a lo explicado con niveles mayores a 250 mg/dL.

De igual manera, la infusión de insulina se hace basándose en la ecuación (7), sin embargo, se redefine la ecuación (2) con la que se obtiene  $U_n$ . La nueva ecuación (2) consiste ahora en:

$$U_n = 0.02 UI * peso \quad (9)$$

La anterior ecuación se deriva de la infusión de insulina base que recomiendan las guías de manejo una vez que se han alcanzado niveles de glucosa de 200 mg/dL en CAD y de 250 mg/dL en EHH, la cual es de 0.02 - 0.05 UI por kilogramo de peso <sup>[5] [7] [8]</sup>. Esta insulina de base se establece bajo la suposición de que al alcanzar esas cifras glucémicas se iniciará una infusión continua de solución glucosada al 5% y cloruro de sodio al 0.45% a razón de 150 - 250 ml/hora, según lo

marcado en las guías de manejo [5] [7] [8], algo que haría elevar la glucosa sérica del paciente, factor que se compensa por la insulina de base [7] [8].

Para tal punto, el sistema regulará la insulina de base para que la glucosa capilar se mantenga cercana a los 220 mg/dL. Asimismo, el sistema sigue tomando en cuenta la insulina circulante en el cuerpo del paciente.

### Programación del algoritmo

Basado en las ecuaciones y estipulaciones antes mencionadas, se programó el algoritmo para el control glucémico utilizando el programa NetBeans IDE 8.2 con el lenguaje de programación Java (Figura 3), haciendo uso de un equipo de cómputo con sistema operativo de 64 bits Windows versión 10, procesador Intel Celeron N400 de 1.10 GHz, y 4GB de memoria RAM.

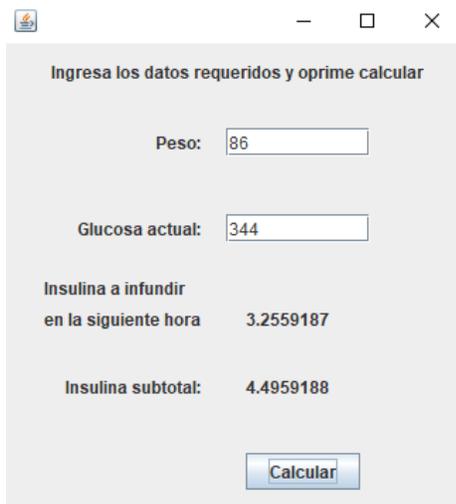


FIGURA 3. Interfaz gráfica del software.

Para probar la funcionalidad del software diseñado se utilizaron los datos obtenidos del manejo de 10 pacientes con diagnóstico de CAD, tratados dentro del servicio de urgencias del Hospital Juárez de México durante los años 2018-2019.

La simulación consistió en utilizar la glucosa inicial reportada, el peso del paciente, y la sensibilidad a la insulina calculada durante cada hora de tratamiento.

Con lo anterior se buscó observar la respuesta del software ante el cambiante estado metabólico de los pacientes. La Figura 4 muestra el método por el cual se realizó la simulación del software.

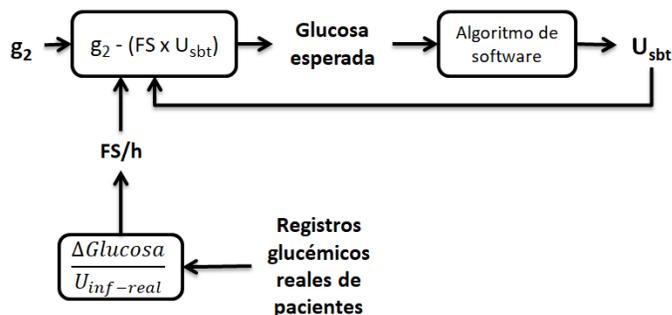


FIGURA 4. Metodología para la simulación.  
 $g_2$ : glucosa actual, FS: sensibilidad a la insulina,  
 FS/h: sensibilidad a la insulina por hora,  $U_{sbt}$ : insulina subtotal,  $U_{inf-real}$ : insulina real infundida.

Se utilizó la ecuación (1) para la obtención de la sensibilidad a la insulina para cada hora de tratamiento, lo que permitió hacer una reproducción del estado metabólico del paciente a lo largo de su tratamiento. Posteriormente, se ingresó al software el peso y glucosa inicial del paciente. Una vez que el software estableció la insulina a infundir durante la siguiente hora se realizaron las predicciones sobre la glucosa esperada (GE), según la sensibilidad a la insulina del paciente durante la hora específica, basado en la siguiente ecuación:

$$GE = g_2 - (FS * U_{sbt}) \tag{10}$$

Esta ecuación se deriva de un despeje y proyección hacia la próxima hora de la ecuación (1) haciendo a  $g_1$  = glucosa esperada, y a insulina usada en la hora anterior =  $U_{sbt}$ . Se utiliza a  $U_{sbt}$  debido a que la glucosa esperada dependerá del total de insulina que existe en el cuerpo del paciente durante la siguiente hora, es decir, la suma entre la insulina infundida y la aún circulante ( $U_{inf} + U_p$ ), que resulta matemáticamente en  $U_{sbt}$ .

Los valores de glucosa esperada se ingresaron al software, repitiéndose el proceso el mismo número de veces que de horas de tratamiento en el servicio de urgencias hasta la resolución de la CAD o hasta el inicio de soluciones glucosadas intravenosa, siempre usando el valor de sensibilidad a la insulina que manejó el paciente en el momento específico del tratamiento.

### Análisis estadístico

Con la finalidad de medir la efectividad del sistema con valores de glucosa  $> 250$  mg/dL, se obtuvo el valor de descenso en la glucosa por hora (tanto en la glucosa real como en la simulada) para cada uno de los 10 casos, calculándose posteriormente el descenso medio de glucosa/hora (DMG), de las mediciones reales y simuladas. Además se evaluó la cantidad de horas necesarias para llevar la glucosa a niveles por debajo de 250 mg/dL en ambos tipos de mediciones, al igual que el número de descensos de glucosa mayores a 100 mg/dL/h.

Para valorar el funcionamiento del sistema en glucosadas  $< 250$  mg/dL se evaluó la existencia de hipoglucemias (glucosa  $< 200$  mg/dL) o hiperglucemias (glucosa  $> 250$  mg/dL después de haber entrado al rango de  $< 250$  mg/dL) en mediciones reales y simuladas.

Se calculó además la cantidad total de insulina real infundida y de insulina simulada.

Finalmente, mediante IBM SPSS Statistics Versión 25 (IBM Corporation, USA) se buscó comparar las medias de las variables cuantitativas con la prueba *t de Student* para muestras relacionadas [24]. Para evaluar si los DMG real o simulada diferían de 50 mg/dL/h, valor establecido como referencia para los DMG, se aplicó la prueba *t de Student* para una muestra con un valor de prueba de 50 mg/dL/h. La comparación de las variables cualitativas binarias se efectuó con la prueba de *McNemar* [24]. En todas las pruebas estadísticas se utilizó un valor  $p < 0.05$  para considerar la existencia de diferencias significativas entre las mediciones evaluadas.

## RESULTADOS Y DISCUSIÓN

La población cuyos registros fueron utilizados en este estudio constó de 5 hombres y 5 mujeres, con una edad media de 36 años con DE 16.32, un peso medio de 71.9 kg con DE 22.42, así como una glucosa inicial media de 485.2 mg/dL con DE 90.69. Dentro de las Figuras 5 y 6 se muestran los descensos de glucosa por hora en las mediciones reales y simuladas, para cada uno de los 10 pacientes.

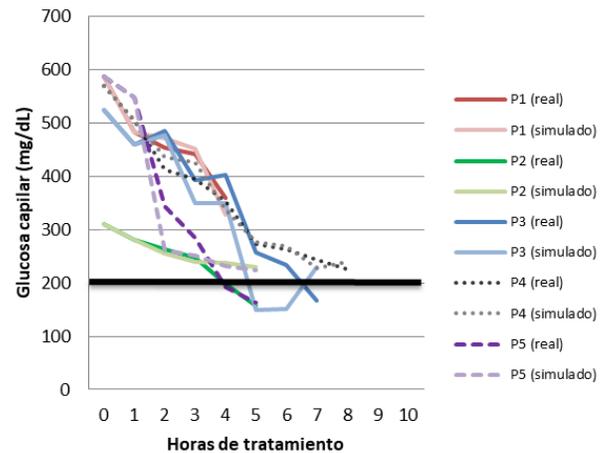


FIGURA 5. Descenso glucémico por hora de pacientes 1 - 5.

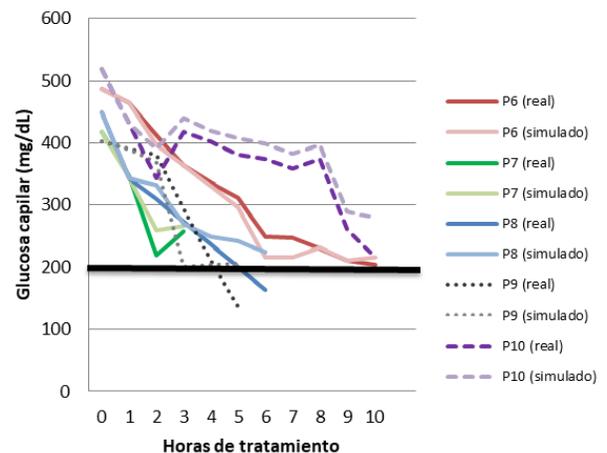
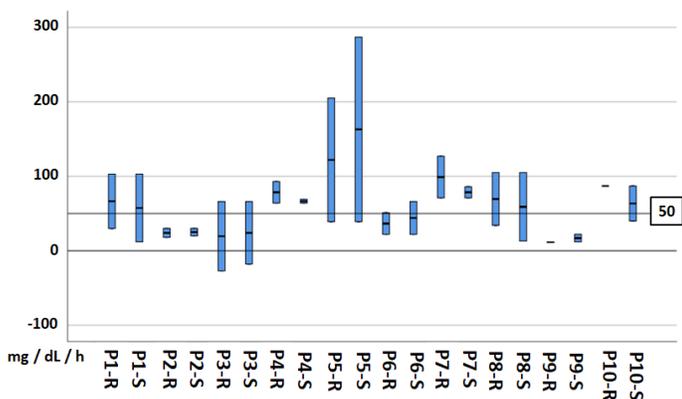


FIGURA 6. Descenso glucémico por hora de pacientes 6 - 10.

Se obtuvo un DMG de 51.94 mg/dL para las mediciones reales, mientras que para las mediciones simuladas el DMG fue de 51.73, no existiendo diferencia estadística entre ambas (Tabla 2). Por otra parte, si bien los DMG para mediciones reales y simuladas no

mostraron diferencia estadística con los 50 mg/dL/h recomendados por las guías de tratamiento [17] ( $p = 0.8$ ), aún así existieron algunos descensos de glucosa por hora que no se apegaron a las recomendaciones, tal y como se aprecia en las Figuras 5 y 6. En la Figura 7 se presenta de manera gráfica la dispersión los descensos de glucosa por hora, tanto en mediciones reales como simuladas. En esta figura se aprecia que las dispersiones de mediciones reales y simuladas resultan similares, es decir, el manejo brindado por médicos y por el algoritmo podría tener las mismas características.



**FIGURA 7. Dispersión en descensos de glucosa por hora en mediciones reales y simuladas.**

**P: Paciente, R: Medición real, S: Medición simulada.**

Dentro de la Tabla 1 se muestra la cantidad total de insulina infundida de manera real y simulada en los pacientes. Dentro de algunas de las simulaciones, el software realiza la recomendación de valores negativos de insulina, debido a que busca generar un aumento en los niveles de glucosa, o contrarrestar la acción de un exceso de insulina circulante. En las sumas totales de insulina se toman en cuenta solo los valores positivos debido a que los negativos tienen otro significado que se comenta dentro de la discusión.

Se encontró una incidencia de hipoglucemias 6 veces menor en las mediciones simuladas, con respecto a las reales, cuya diferencia resultó estadísticamente significativa. Por otra parte, hubo una disminución del

**TABLA 1. Insulina total infundida y simulada**

Px	P1	P2	P3	P4	P5
IR	57 UI	78 UI	82 UI	63 UI	51 UI
IS	42 UI	38.8 UI	51.4 UI	56.3 UI	27.1 UI
Px	P6	P7	P8	P9	P10
IR	154 UI	19 UI	65 UI	36 UI	165 UI
IS	97.5 UI	21.1 UI	34.9 UI	28.8 UI	112 UI

P: paciente, IR: insulina real, IS: insulina simulada.

33.7% en la cantidad de insulina necesaria para alcanzar las metas de tratamiento. No se encontró diferencia estadística entre las mediciones reales y simuladas en cuanto al DMG, así como en el número de horas de tratamiento necesarias para obtener glucemias menores a 250 mg/dL y en descensos de glucosa mayores a 100 mg/dL/h. Como se comentó anteriormente, tampoco se encontró diferencia estadística entre los DMG y el valor de prueba de 50 mg/dL de glucosa, meta de descenso glucémico por hora según las guías de tratamiento, lo que demuestra un apego a las guías de tratamiento [17]. En la Tabla 2 se resumen los resultados estadísticos de las pruebas de *McNemar* y *t de Student* para estas variables. Con estos resultados no solo se demuestra que el algoritmo presentado logra un manejo similar al brindado por el personal médico, sino que también podría generar mejoras en la frecuencia de hipoglucemias e insulina necesaria para el tratamiento, por lo que su utilización dentro de dispositivos automatizados de manejo glucémico para CAD y EHH resultaría viable.

Si bien dentro de la literatura reciente existen numerosos trabajos que proponen sistemas de control automatizado para el manejo glucémico de pacientes diabéticos [11][12][13][14], el presente trabajo buscó innovar en algunos puntos como son: la aplicación de estos sistemas en complicaciones agudas de la diabetes, su aplicación en el medio intrahospitalario y el uso de la sensibilidad a la insulina como parte de las variables de entrada para el control glucémico por parte del software controlador.

TABLA 2. Pruebas estadísticas

Prueba t para muestras relacionadas			
Variable	Media	T	Sig.
DMG Real	51.94	-0.58	0.955
DMG Simulada	51.73		
Descensos >100mg/dL/h reales	0.7	-0.557	0.591
Descensos >100mg/dL/h simulados	0.8		
Insulina total real	77.00 UI	4.164	0.002
Insulina total simulada	50.99 UI		
Horas necesarias para GR<250 mg/dL	5.1 h	-0.802	0.443
Horas necesarias para Gs<250 mg/dL	5.3 h		
Prueba t para una muestra (valor de prueba = 50 mg/dL)			
Variable	Media	T	Sig.
DMG Real	51.94	0.259	0.802
DMG Simulada	51.73	0.194	0.851
Prueba McNemar			
Variable	Frecuencia	Sig.	
Hipoglucemias reales	6	0.031	
Hipoglucemias simuladas	1		
Hiperoglucemias reales	1	1.000	
Hiperoglucemias simuladas	0		

DMG: descenso medio de glucosa, GR: glucosa real, GS: glucosa simulada, T: valor t, Sig: significancia estadística (valor p).

Según los datos arrojados por el análisis estadístico, el software genera DMG similares a cuando los niveles glucémicos son manejados por un médico, reduciendo además la incidencia de hipoglucemias. Esto da lugar a la suposición de que es posible la aplicación de este software dentro de un dispositivo biomédico autónomo para el manejo glucémico de pacientes con CAD sin la necesidad de la intervención del personal médico. Lo anterior resulta en una gran ventaja, ya que reduciría el tiempo que necesita invertir el servicio de urgencias en este tipo de pacientes, un punto de gran beneficio principalmente en unidades hospitalarias de alta saturación y poco personal disponible. Asimismo, abre la posibilidad de una reducción en las complicaciones derivadas del tratamiento con insulina, aumentando la seguridad en el manejo de estos pacientes.

Por otra parte, en los resultados de la simulación se observó que el software, a menudo, recomienda administrar cifras negativas de insulina: sin embargo, de manera real no es posible, por lo que es de suponerse que en estos casos sería necesaria la administración de volúmenes específicos de solución glucosada intravenosa, ante la solicitud del sistema de un efecto hiperglucémico, contrario a lo generado por la insulina. Esta tarea debería ser realizada por el mismo equipo biomédico para conservar su autonomía; es decir, se requiere de una bomba de infusión dual de insulina y glucosa, similar a lo propuesto por Jacobs *et al.* con su páncreas artificial dual de insulina-glucagón [25]. La cantidad de glucosa intravenosa a infundir deberá depender de la glucosa a aumentar en la siguiente hora, es decir, del error proporcional, obtenido mediante un despeje de la ecuación (1) con respecto a  $\Delta$ Glucosa, así como de la farmacocinética de la glucosa en el cuerpo humano [26]. Este último punto no se evalúa dentro de este trabajo debido a que no es el objetivo, no obstante, es un aspecto a resolver para la implementación del algoritmo en una fase clínica posterior.

Un resultado interesante en la simulación fue la reducción estadísticamente significativa de la cantidad necesaria de insulina para alcanzar las metas terapéuticas. Ello puede deberse a que el software toma en cuenta la sensibilidad a la insulina y la insulina circulante, logrando así aprovechar los momentos con alta sensibilidad a la insulina para generar descensos glucémicos apropiados para el estado metabólico del paciente, a la vez que evita infundir más insulina de la necesaria cuando aún existe insulina circulante en el organismo. Lo anterior resulta en otro potencial beneficio de la implementación del software en el manejo de pacientes con CAD, una posible reducción en el costo de la atención médica de los mismos.

Desafortunadamente no se encontró diferencia estadística entre los descensos de glucosa > 100 mg/dL entre las mediciones reales y simuladas, debido a que

tales eventos se derivan de sucesos poco predecibles en el metabolismo de los pacientes que resultan en cambios drásticos en la sensibilidad a la insulina. La solución ante este problema es un monitoreo glucémico más frecuente, que permita al software notar a tiempo los cambios en la sensibilidad a la insulina, lo cual sería posible con la implementación de un monitoreo glucémico continuo que permita al software la toma de decisiones en periodos más cortos de tiempo. De tal manera que podrían generarse DMG más estables y con menor variación entre horas, lo que haría posible su aplicación no solo en pacientes adultos, sino también en pacientes pediátricos, donde el manejo glucémico debe ser más estricto dada la mayor facilidad con que generan edema cerebral, resultado de variaciones fuertes en la osmolaridad sanguínea [26].

### CONCLUSIONES

El algoritmo de control automatizado evaluado en el presente trabajo intenta brindar una opción de manejo que permita al médico ahorrar tiempo en el tratamiento de estos pacientes, así como mejorar los resul-

tados terapéuticos y disminuir el riesgo de complicaciones derivadas del mismo. La principal limitación del estudio fue la imposibilidad de realizar pruebas del software con pacientes reales, sin embargo, la simulación fue un punto necesario debido a que: 1) no existe literatura sobre aplicaciones de sistemas de control automatizado en el manejo de estas patologías, y 2) el estado crítico de los pacientes vuelve poco ético su aplicación en humanos sin resultados previos de su funcionalidad. Dentro del trabajo se comprobó que el propio sistema podría ser capaz de lograr un manejo glucémico similar al brindado por el personal médico en el tratamiento de la CAD, apegándose a las guías de tratamiento, además de evitar hipoglucemias y generar un menor gasto de insulina durante la terapéutica. Lo anterior abre la puerta a una posible utilización de este sistema dentro de un dispositivo biomédico autónomo para el manejo glucémico de pacientes con complicaciones agudas de la diabetes dentro del servicio de urgencias, pudiendo así acercar a la medicina un paso más hacia la automatización de la terapéutica en el paciente crítico.

## REFERENCIAS

- [1] Fayman M, Pasquel FJ, Umpierrez G. Management of hyperglycemic crises. *Med Clin N Am.* 2017; 103(3): 587-606. DOI: [10.1016/j.mcna.2016.12.011](https://doi.org/10.1016/j.mcna.2016.12.011)
- [2] Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic crises: Diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS). *Endotext* [Internet]. 2018 May. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279052/>
- [3] Escobedo J, Rico B. Incidencia y letalidad de las complicaciones agudas y crónicas de la diabetes mellitus en México. *Salud Públ Méx.* 1996; 38(4): 236-242.
- [4] Domínguez M, Calderón MA, Matías R. Características clínico epidemiológicas de las complicaciones agudas de la diabetes en el servicio de urgencias del Hospital General de Atizapán. *Rev Fac Med.* 2013; 56(2): 25-36.
- [5] Karslioglu-French E, Donihi AC, Korytkowski MT. Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients. *BMJ.* 2019; 365: I1114. DOI: [10.1136/bmj.i1114](https://doi.org/10.1136/bmj.i1114)
- [6] Kibachi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care.* 2009; 32(7): 1335-1345. DOI: [10.2337/dc09-9032](https://doi.org/10.2337/dc09-9032)
- [7] Ghimire P, Dhamoon AS. Ketoacidosis. *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK534848/>
- [8] Dhatariya KK, Vellanki P. Treatment of diabetic ketoacidosis (DKA)/ Hyperglycemic hyperosmolar state (HHS): Novel advances in the management of hyperglycemic crises (UK versus USA). *Curr Diab Rep.* 2017; 17(5). DOI: [10.1007/s11892-017-0857-4](https://doi.org/10.1007/s11892-017-0857-4)
- [9] Goguen J, Gilbert J. Hyperglycemic emergencies in adults. *Can J Diabetes.* 2018; 42: S109-S114. DOI: [10.1016/j.cjcd.2017.10.013](https://doi.org/10.1016/j.cjcd.2017.10.013)
- [10] Fernández J, Galindo C, Barbacho J, Luque A. Automatic control systems in biomedical engineering. 1a ed. Springer International Publishing; 2018. DOI: [10.1007/978-3-319-75717-9](https://doi.org/10.1007/978-3-319-75717-9)
- [11] Thabit H, Hovorka R. Closed-loop insulin delivery in type 1 diabetes. *Endocrinol Metab Clin N Am.* 2012; 41: 105-117. DOI: [10.1016/j.ecl.2011.12.003](https://doi.org/10.1016/j.ecl.2011.12.003)
- [12] Waugh N, Adler A, Craigie I, Omer T. Closed loop system in type 1 diabetes. *BMJ.* 2018; 361: K1613. DOI: [10.1136/BMJ.K1613](https://doi.org/10.1136/BMJ.K1613)
- [13] Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes.* 2006; 55(12): 3344-3350. DOI: [10.2337/db06-0419](https://doi.org/10.2337/db06-0419)
- [14] Huyett LM, Dassau E, Zisser HC, Doyle FJ. Design and evaluation of a robust PID controller for a fully implantable artificial pancreas. *Ind Eng Chem Res.* 2015; 54(42): 10311-10321. DOI: [10.1021/acs.iecr.5b01237](https://doi.org/10.1021/acs.iecr.5b01237)
- [15] Hu R, Li C. An improved PID algorithm based in insulin-on-board estimate for blood glucose control with type 1 diabetes. *Comput Math Method M.* 2015; 2015: 281589. DOI: [10.1155/2015/281589](https://doi.org/10.1155/2015/281589)
- [16] Pisker JE, Lee JB, Daussau E, Seborg DE, Bradley PK, Gondhalekar R, et al. Randomized crossover comparison of personalized MPC and PID control algorithms for the artificial pancreas. *Diabetes Care.* 2016; 39(7): 1135-1142. DOI: [10.2337/dc15-2344](https://doi.org/10.2337/dc15-2344)
- [17] Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JJ, Wall BM. Management of hyperglycemic crisis in patients with diabetes. *Diabetes Care.* 2001; 24(1): 131-153. DOI: [10.2337/diacare.24.1.131](https://doi.org/10.2337/diacare.24.1.131)
- [18] Luzi L, Barrett FJ, Groop LC, Ferrannini F, DeFronzo RA. Metabolic effects of low-dose insulin therapy on glucose metabolism in diabetic ketoacidosis. *Diabetes.* 1988; 37(11): 1470. DOI: [10.2337/diab.37.11.1470](https://doi.org/10.2337/diab.37.11.1470)
- [19] Davidson PC, Hebblewhite HR, Steed RD, Bode BW. Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate to insulin ratio. *Endocr Pract.* 2008; 14(9): 1095-1101. DOI: [10.4158/EP.14.9.1095](https://doi.org/10.4158/EP.14.9.1095)
- [20] Steil GM, Palerm CC, Kurtz N, Voskanyan G, Roy A, Paz S, Kandeel FR. The effect of insulin feedback on closed loop glucose control. *J Clin Endocrinol Metab.* 2011; 96(5): 1402-1408. DOI: [10.1210/jc.2010-2578](https://doi.org/10.1210/jc.2010-2578)
- [21] Rasmussen CH, Roge RM, Ma Z, Thomsen M, Thorisdottir RL, Chen J-W, et al. Insulin aspart pharmacokinetics: An assessment of its variability and underlying mechanisms. *Eur J Pharm Sci.* 2014; 62: 65-75. DOI: [10.1016/j.ejps.2014.05.010](https://doi.org/10.1016/j.ejps.2014.05.010)
- [22] Soeborg T, Rasmussen CH, Mosekilde E, Colding-Jorgensen M. Absorption kinetics of insulin after subcutaneous administration. *Eur J Pharm Sci.* 2009; 36(1): 78-90. DOI: [10.1016/j.ejps.2008.10.018](https://doi.org/10.1016/j.ejps.2008.10.018)
- [23] Mosekilde E, Jensen KS, Binder C, Pramming S, Thorsteinsson B. Modeling absorption kinetics of subcutaneous injected soluble insulin. *J Pharm Biopharm.* 1989; 17(1): 67-87. DOI: [10.1007/bf01059088](https://doi.org/10.1007/bf01059088)
- [24] Flores E, Miranda MG, Villasis MA. El protocolo de investigación VI: cómo elegir la prueba estadística adecuada. *Estadística inferencial. Rev Alerg Mex.* 2017; 64(3): 364-370. DOI: [10.29262/ram.v64i3.304](https://doi.org/10.29262/ram.v64i3.304)
- [25] Jacobs PG, Youssef JE, Castle JR, Engle JM, Branigan DL, Johnson P, et al. Development of a fully automated closed loop artificial pancreas control system with dual pump delivery of insulin and glucagon. 33rd Annual International Conference of the IEEE EMBS; 2011 Aug 30 - Sep 03; Massachusetts, USA: IEEE; 2011. DOI: [10.1109/iembs.2011.6090127](https://doi.org/10.1109/iembs.2011.6090127)
- [26] Raghupathy P. Diabetic ketoacidosis in children and adolescents. *Indian J Endocrinol Metab.* 2015 (Suppl 1); S55-S57. DOI: [10.4103/2230-8210.155403](https://doi.org/10.4103/2230-8210.155403)

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## Regularized Hypothesis Testing in Random Fields with Applications to Neuroimaging

### Pruebas de Hipótesis Regularizadas en Campos Aleatorios con Aplicaciones a Neuroimágenes

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#### ABSTRACT

The task of determining for which elements of a random field (e.g., pixels in an image) a certain null hypothesis may be rejected is a relevant problem in several scientific areas. In the current contribution, we introduce a new method for performing this task, the regularized hypothesis testing (RHT) method, focusing on its use in neuroimaging research. RHT is based on the formulation of the hypothesis testing task as a Bayesian estimation problem, with the previous application of a Markovian random field. The latter allows for the incorporation of local spatial information and considers different noise models, including spatially correlated noise. In tests on synthetic data showing regular activation levels on uncorrelated noise fields, RHT furnished a true positive rate (TPR) of 0.97, overcoming the state-of-the-art morphology-based hypothesis testing (MBHT) method and the traditional family-wise error rate (FWER) method, which afforded 0.93 and 0.58, respectively. For fields with highly correlated noise, the TPR provided by RHT was 0.65, and by MBHT and FWER was 0.35 and 0.29, respectively. For tests utilizing real functional magnetic resonance imaging (fMRI) data, RHT managed to locate the activation regions when 60% of the original signal were removed, while MBHT located only one region and FWER located none.

**KEYWORDS:** Regularized hypothesis test; Markovian random fields; Bayesian estimation; functional Magnetic resonance imaging.

## RESUMEN

En varias áreas científicas aparece el problema de determinar los elementos de un campo aleatorio (por ejemplo, píxeles en una imagen) en los que se puede rechazar una cierta hipótesis nula. En este artículo presentamos un nuevo método para realizar esta tarea, centrado en aplicaciones para investigación de neuroimagen. Nuestra propuesta se basa en la formulación de pruebas de hipótesis como un problema de estimación Bayesiana, usando como a priori un campo aleatorio Markoviano, que permite incorporar información espacial local y considera diferentes modelos de ruido, incluido el ruido correlacionado espacialmente. Para pruebas en datos sintéticos con niveles de activación regulares sobre campos de ruido no correlacionado, nuestro método obtiene una tasa de verdaderos positivos (TPR) de 0.97, superando al método del estado del arte MBHT y al método de control FWER que obtienen 0.93 y 0.58 respectivamente; para campos con ruido altamente correlacionado, nuestro método obtiene un TPR de 0.65, mientras que MBHT y FWER obtienen 0.35 y 0.29 respectivamente. Para pruebas con datos reales de fMRI, nuestro método localiza las regiones de activación cuando removemos 60% de la señal original, mientras que MBHT no localiza región alguna y FWER localiza una de las dos regiones.

**PALABRAS CLAVE:** Prueba de hipótesis regularizada; campo aleatorio Markoviano; estimación Bayesiana; Imágenes de Resonancia Magnética Funcional.

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## INTRODUCTION

In areas of scientific research where imaging is involved (e.g., neuroimaging, remote sensing, etc.), it is often necessary to test statistical hypotheses at each element of a 2 or 3-dimensional field of sites (pixels or voxels). The purpose is to determine the set of sites at which the response to a given experiment may be different from baseline, or whether it is significantly correlated with another parameter.

For instance, researchers in the area of neuroscience typically conduct studies to identify the area of the brain responsible for a certain cognitive task. The experiments are composed of stimulus and rest periods applied to a single subject or several people <sup>[1] [2] [3] [4] [5]</sup>, applying a functional imaging approach such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). Subsequently, the regions of voxels with a significant degree of activation have to be detected by performing simultaneous hypothesis tests over 2 or 3-dimensional measurements.

Because hundreds of thousands of comparisons are made at the same time, the well-known problem of multiple comparisons appears <sup>[6] [7]</sup>. The researcher is thus obliged to seek a solution to the resulting increase in the percentage of false positives (type I errors). A popular family of approaches to deal with this problem are the so-called pointwise (PW) methods, which utilize some type of thresholding technique to control the family-wise error rate (FWER) <sup>[6] [8]</sup>. Although they present a simple and easy to interpret solution, there is a high rate of type I errors.

Some authors address the problem through the Gaussian random fields (GRF) theory <sup>[9] [10]</sup>, under the assumption that the spatial correlation of the data is known or can be estimated. Since this is not true in practice <sup>[11]</sup>, a smoothing filter is applied to the raw images to ensure that these assumptions are met. Such a pre-processing process causes a loss of spatial resolu-

tion <sup>[5]</sup>. On the other hand, threshold-free methodologies <sup>[12]</sup> employ erosion and dilatation morphological operators with a set of structuring elements of various sizes to detect regions exhibiting moderate activation levels and wide spatial size. However, their results are subject to the form of the structuring elements, which is determined arbitrarily.

In the current contribution, we propose a new method, denominated the regularized hypothesis testing (RHT) method. It is based on the formulation of the hypothesis testing task as a Bayesian estimation problem using a Markovian random field (MRF) to incorporate local spatial information. Firstly, mention is made of the state-of-the-art methods available to solve the problem of hypothesis testing in 2 and 3-dimensional fields. Thereafter, RHT is explained along with related theoretical considerations. The problem of parameter selection is addressed by proposing two algorithms for automatic calibration. Having laid out the new method, it is validated by experiments with simulated and real data. Finally, the results are discussed and conclusions are drawn.

## Theoretical framework

The problem of testing statistical hypotheses at each element of a 2 or 3-dimensional field can be conceived as the following general problem:

Given a set  $\mathcal{L}$  of sites, there is a statistic  $\mathbf{T}(u)$  defined for each site  $u \in \mathcal{L}$  for which one wishes to test a null hypothesis ( $H_0$ ). According to this hypothesis, all elements  $\mathbf{T}(u)$  are furnished by the distribution  $P_0(\mathbf{T})$  (the null distribution).  $H_0$  is assumed to be of the form:

$$H_0 = \bigcap_{u \in \mathcal{L}} H_{0u}, \quad (1)$$

where  $H_{0u}$  is a marginal null hypothesis about the probability distribution of the measurements at site  $u$ . At  $H_{0u}$ , consequently,  $\mathbf{T}(u)$  is generated by  $P_0$ . In the active region,  $\mathcal{A}$  is defined as the set of sites  $u$  where

$H_{0u}$  does not hold, thus affirming the alternative hypothesis  $H_{1u}$ . The problem then is to find an estimate  $\mathcal{A}$  for the set  $\mathcal{A}$  (note:  $\mathcal{A}$  and  $\hat{\mathcal{A}}$  may be empty).

Once a method is selected, its performance must be evaluated with standard tools. Some very common tools that will be used presently are described.

1. The false positive rate (FPR) is defined by:

$$FPR = E \left[ \frac{|\mathcal{A}^c \cap \hat{\mathcal{A}}|}{|\mathcal{A}^c|} \right], \quad (2)$$

where  $\mathcal{A}^c$  is the complement of the active region  $\mathcal{A}$ ,  $|\cdot|$  denotes the cardinality of a set and  $E[\cdot]$  refers to the expected value of a random variable.

It is also possible to define FPR for elements that are not adjacent to the boundary of the active region:

$$FPR_r = E \left[ \frac{|(D_r \mathcal{A})^c \cap \hat{\mathcal{A}}|}{|(D_r \mathcal{A})^c|} \right], \quad (3)$$

where the  $r$ -dilation  $D_r$  of  $\mathcal{A}$  is defined as:

$$D_r \mathcal{A} = \left\{ u \in \mathcal{L} : \min_{v \in \mathcal{A}} \|u - v\| \leq r \right\}. \quad (4)$$

This measure is defined for two reasons. Firstly, the boundary of the active region is usually not well localized, since the activation level often decreases slowly as one moves away from  $\mathcal{A}$ . Secondly, the methods that consider the neighborhood of each element for estimating  $\mathcal{A}$  likely indicated an increased number of false positives nearby to the boundary of the active region. If most false positives are of this kind, they should have less impact on the measured performance than the false positives disconnected from  $\mathcal{A}$ .

Thus,  $FPR_r$  could be a better performance measure in such a case.

2. The true positive rate (TPR), also called sensitivity, is defined by:

$$TPR = E \left[ \frac{|\mathcal{A} \cap \hat{\mathcal{A}}|}{|\hat{\mathcal{A}}|} \right], \quad (5)$$

denoting the expected proportion of sites correctly estimated as the activation region.

3. The family-wise error rate (FWER) is defined by:

$$FWER = Pr(\hat{\mathcal{A}} \neq \emptyset | \mathcal{A} = \emptyset), \quad (6)$$

representing the probability of having at least one false positive, given that the activation region is empty.

4. The false discovery rate (FDR) is defined by:

$$FDR = E \left[ \frac{|\mathcal{A}^c \cap \hat{\mathcal{A}}|}{|\hat{\mathcal{A}}|} \right] = \frac{W \cdot FPR}{|\mathcal{A}| \cdot FPR + TPR}, \quad (7)$$

with  $W = (|\mathcal{L}| - |\mathcal{A}|) / |\mathcal{A}|$ ,

portraying the proportion of wrongly rejected null hypotheses in  $\hat{\mathcal{A}}$ .

Some of these measures can be combined. For example, a widely accepted way of characterizing the performance of a method is through the receiver operating characteristic (ROC) curve [13], which indicates, for a fixed  $\mathcal{A}$ , the maximum attainable TPR for any given maximum allowable FPR. For one-sided tests, the maximum TPR is generally an increasing function of the maximum allowable FPR.

To construct the curve, the true region  $\mathcal{A}$  and the corresponding activation level  $a = E[T(u)]$ ,  $u \in \mathcal{A}$  must be known. Then, the study of a method that depends on a parameter  $\theta$  involves setting a value for  $\theta$  to obtain a point on the ROC curve. The parameter acts as a cut-

off point to distinguish between the sites considered positives or negatives. Take as an example the methods based on the following computation:

$$\hat{\mathcal{A}} = \{ u : pv(u) \leq \theta \}, \quad (8)$$

where  $pv(u)$  depicts the p-value of  $\mathbf{T}(u)$  and therefore  $pv(u) = 1 - P_0(\mathbf{T}(u))$ . This class of methods, denominated PW, encompasses most of the standard methods. They differ from each other only in the way the threshold  $\theta$  is computed (note: all PW methods have the same ROC curve, regardless of the way  $\theta$  is computed). Thus, for the application of the threshold based on a significance level  $\alpha$ , without correction for multiple hypotheses (uncorrected method), it holds that  $\theta = \alpha$ . For the FWER method [6] [8] [14], with significance level  $\alpha_{FWER}$ , it follows that:

$$\theta = 1 - P_0((P_0^M)^{-1}(1 - \alpha_{FWER})), \quad (9)$$

where  $P_0^M$  is the distribution of  $\max_{u \in \mathcal{L}} \mathbf{T}(u)$  under  $H_0$ . Consequently, FWER can be controlled by choosing as the threshold the value located at the  $(1 - \alpha_{FWER})$  portion of the right side of  $P_0^M$ . For an elaborate discussion on the association of FWER with the maximum statistical value, see Pantazis [15].

In the case of FDR, with a significance level  $\alpha_{FDR}$  [16], the procedure for finding the threshold  $\theta$  begins with ordering the individual p-values of sites  $u \in \mathcal{L}$  from the largest to the smallest. Accordingly,  $pv(u_1) \geq pv(u_2) \geq \dots \geq pv(u_N)$  with  $N = |\mathcal{L}|$ . Let  $k$  be the index of the first site on the list, at which the p-value is less than or equal to the desired FDR proportion. Hence,

$$pv(u_k) \leq \frac{k}{N} \alpha_{FDR},$$

and  $\theta$  is set as:

$$\theta = pv(u_k). \quad (10)$$

For more details on the method, consult Benjamini [17]. Alternatively, given a desired value  $\epsilon$  for  $FPR_{\max}$ ,  $\theta$  can simply be set as  $\epsilon$  (e.g.,  $\epsilon = 10^{-5}$ ). If the local hypotheses  $H_{0u}$  are independent, this is equivalent to the application of the standard PW method without correction for multiple hypotheses, but with low level of significance  $\alpha = \epsilon$ . Since (as mentioned) the maximum TPR is an increasing function of FPR, the value of  $\theta^* = \epsilon$  will be the one that maximizes the TPR while keeping FPR under control:

$$\max TPR \text{ subject to } FPR \leq \epsilon, \quad (11)$$

where  $\epsilon$  is a user-specified small positive number. Although the actual ROC curve for a given problem is unknown (because it depends on the values of  $\mathbf{T}(u)$  for  $u \in \mathcal{A}$ ), it is possible to specify the value of  $\epsilon$ . Thus, the optimal PW method, according to Eq. (11) with  $\theta = \theta^*$ , will correspond to the UC method with  $\alpha = 1 - \epsilon$ . It may be applied if the field of p-values, or equivalently the field  $P_0(\mathbf{T}(u))$ ,  $u \in \mathcal{L}$ , is known. Such fields can be estimated either theoretically or by non-parametric empirical means (e.g., permutation or re-sampling procedures) [18] [19]. The optimal PW method will be denoted by  $PW^*(\epsilon)$ .

The signal-to-noise ratio (SNR) [20] is defined as:

$$SNR = \frac{\min_{u \in \mathcal{A}} \mathbf{T}(u)}{\sigma_0}, \quad (12)$$

where  $\sigma_0$  is the variance of  $\mathbf{T}$  under  $H_0$  and the minimum activation level in  $\mathbf{T}$  has been arbitrarily assigned as the information signal. This represents the worst-case scenario in which the entire region  $\mathcal{A}$  has a minimum value. On the other hand, the mean activation level or the amplitude could also be employed, as discussed by Welvaert and Rosseel [17] and Acosta-Franco et al. [5]. For low values of SNR, the value of TPR obtained with  $PW^*(\epsilon)$  in the corresponding PW ROC curve is usually low for reasonable values of  $\epsilon$ .

Consequently, PW methods have low sensitivity and the estimated  $\hat{\mathcal{A}}$  is too conservative.

Hence, more sensitive methods must be developed that are able to accurately reflect the active regions, which in most cases consist of clusters of several contiguous elements of  $\mathcal{L}$  and not of isolated elements. Customarily, these methods use the field  $\mathbf{T}$  as a starting point for the generation of a new field  $\hat{\mathbf{T}}$ . The new statistic takes the spatial correlation of  $\mathcal{A}$  into account, and then processes  $\hat{\mathbf{T}}$  with a PW method as before. For example,  $\hat{\mathbf{T}}$  may refer to the size or mass of a cluster of arc-connected elements ( $u$ ) with values of  $\mathbf{T}$  above a certain threshold [21].

However, this approach has some drawbacks, one being that the results depend strongly on the value of the selected threshold, and in general no principled way exists to make such a selection. Some variants of the method alleviate the problem to a certain extent by computing  $\hat{\mathbf{T}}$  as a weighted combination of cluster sizes obtained with different thresholds. Another problem is the loss of interpretability, since in many cases the significance of the statistic sought is directly related to the activation level (i.e., the value of  $\mathbf{T}$ ), and to the extension of supra-threshold clusters.

A distinct approach was developed to address these problems, being the morphology-based hypothesis testing (MBHT) method [12]. It involves the computation of  $\hat{\mathbf{T}}$  as a combination of the results found when applying a set of  $K$  morphological erosions with different sizes of structuring elements to the field  $\mathbf{T}$ . The statistics are calculated as:

$$\mathbf{T}_k(u) = \min_{v \in W_k(u)} \mathbf{T}(v), \text{ for } k = 1, \dots, K, \quad (13)$$

where  $W_k(u)$  denotes the structuring element  $k$  (e.g., a circle of radius  $r_k$ ) centered at  $u$ . Then, these values are integrated into the statistic  $\mathbf{T}$ :

$$\hat{\mathbf{T}}(u) = \max\{P_{01}(\mathbf{T}_1(u)), \dots, P_{0K}(\mathbf{T}_K(u))\}, \quad (14)$$

where  $P_{0k}$  is the null distribution of the statistic  $\mathbf{T}_k$ . Afterwards, the optimal PW procedure can be applied to the field  $\hat{\mathbf{T}}$  as detailed above.

The results of this approach are competitive with those based on supra-threshold cluster statistics [12] and allow a clearer interpretation. Once again, the disadvantage is that the results may depend on the shape of the structuring elements, and for their selection no principled solution exists.

In the current contribution, the approach introduced is capable of overcoming these difficulties. It formulates the hypothesis testing task as a Bayesian estimation problem, with an MRF previously applied to the active regions, thus implementing a prior constraint on the spatial contiguity of  $\mathcal{A}$ . For the application of a Gaussian Markov random field (GMRF) for fMRI data analysis, see Mejia et al. and the references therein [3].

The new scheme proved to have better performance than PW methods, while maintaining interpretability. It also has better performance than MBHT, and does not require the selection of any particular shape for the structuring elements.

### The regularized hypothesis testing method

In RHT, the hypothesis testing problem is written in terms of an image segmentation problem, which is solved by using a Bayesian estimation framework. First, the hypothesis testing formulation is explained. The procedure is laid out for calculating the prior distributions of sites and the likelihood that they belong to an active region. Subsequently, an approximation algorithm for finding the maximum a posterior probability (MAP) estimate is established. Finally, the parameter selection problem is addressed.

## Hypothesis testing formulation

Hypothesis testing may be formulated as a binary segmentation problem. Accordingly, given the set of sites  $\mathcal{L}$ , the problem is reduced to partitioning  $\mathcal{L}$  into non-overlapping cohesive regions  $\mathcal{A}_0, \mathcal{A}_1$ , such that the activation level in region  $\mathcal{A}_0$  is zero, and in region  $\mathcal{A}_1$  is greater than or equal to a known constant  $a_1$ . Hence,  $\mathcal{A}_0 \cap \mathcal{A}_1 = \emptyset$  and  $\mathcal{L} = \mathcal{A}_0 \cup \mathcal{A}_1$ , where  $\mathcal{A} \stackrel{\text{def}}{=} \mathcal{A}_1$  is the active region, and therefore  $\mathcal{A}_0 = \mathcal{A}^c$ .

Let  $\mathbf{c}$  be an unknown discrete label field that identifies the partitions of  $\mathcal{L}$ , defining  $\mathbf{c}(u) \in \mathcal{K} \stackrel{\text{def}}{=} \{0,1\}$  and  $\mathbf{c}(u) = k$  if  $u \in \mathcal{A}_k$ , for each  $u \in \mathcal{L}$ . Thus,  $a_{\mathbf{c}(u)}$  depicts the activation level at site  $u$  (note:  $a_0 = 0$ ).

Without loss of generality, the activation level in  $\mathcal{A}_1$  is assumed to be equal to  $a_1$ , since this represents a worst case in terms of the desired false positive control in the estimation of  $\mathcal{A}$ . Considering  $\mathbf{T}$  as the field formed by the statistics  $\mathbf{T}(u)$  for all  $u \in \mathcal{L}$ , the following observation model is proposed:

$$\mathbf{T} = a_1 \mathbf{c} + n, \quad (15)$$

where  $\mathbf{n}$  is a noise field showing distribution  $P_{\mathbf{n}}(\mathbf{n})$ , with:

$$P_{\mathbf{n}}(\mathbf{n}) = \frac{1}{Z_{\mathbf{n}}} \exp(-U_{\mathbf{n}}(\mathbf{n})), \quad (16)$$

where  $Z_{\mathbf{n}}$  is a normalization constant and  $U_{\mathbf{n}}(\mathbf{n})$  is a so-called energy function. Then, the likelihood  $P(\mathbf{T}|\mathbf{c})$  is furnished as:

$$\begin{aligned} P(\mathbf{T}|\mathbf{c}) &\stackrel{\text{def}}{=} \frac{1}{Z_{\mathbf{T}|\mathbf{c}}} \exp(-U_{\mathbf{T}|\mathbf{c}}(\mathbf{c})) \\ &= P_{\mathbf{n}}(\mathbf{T} - a_1 \mathbf{c}), \end{aligned} \quad (17)$$

where  $Z_{(\mathbf{T}|\mathbf{c})}$  is a normalization constant. It is important to find an estimate that considers the spatial correlation in both the noise field  $\mathbf{n}$  and the label field  $\mathbf{c}$ .

As the real statistic  $\mathbf{T}$  is obtained through a regression analysis of data provided by a model, it could take on a positive or negative value (depending on the choice of the statistic), resulting in positive or negative differences— activation regions— of the data with respect to the model. Zero-value regions would still portray sites where there is no activation, and the distribution of values of field  $\mathbf{n}$  would be determined by the selection of the statistic  $\mathbf{T}$ . Hereafter, a noise model is presented as a GMRF. In later sections, we remove this assumption by introducing a procedure for standardizing the noise field in order to map noise fields ranging from arbitrary distributions to standard normal distributions.

## Noise field model

For the noise field  $\mathbf{n}$ , a GMRF model was employed, taking the form of Eq. (16) with:

$$U_{\mathbf{n}}(\mathbf{n}) = \frac{1}{2} \gamma \sum_{u \in \mathcal{L}} \mathbf{n}(u)^2 + \tau_1 \sum_{\langle u,v \rangle} (\mathbf{n}(u) - \mathbf{n}(v))^2, \quad (18)$$

where  $\gamma > 0$  is a scale parameter,  $\mathbf{n}(u)$  is the value of the field  $\mathbf{n}$  in site  $u$ , and  $\mathbf{n}(v)$  is the value of the field  $\mathbf{n}$  in a neighboring site  $v$ . The parameter  $\tau_1 \geq 0$  is related to the spatial correlation of the field  $\mathbf{n}$  and the second term added to the first is taken from all pairs of neighboring sites  $\langle u, v \rangle$  in the image.

When  $\tau_1 = 0$  and  $\gamma = 1$ , the formulation is reduced to a Gaussian white noise model with zero mean and unit variance (the ‘‘Parameter Selection’’ section explains other types of noise fields). With such a model, the likelihood takes the form of Eq. (17), being:

$$\begin{aligned} U_{\mathbf{T}|\mathbf{c}}(\mathbf{c}) &= \frac{1}{2} \gamma \sum_{u \in \mathcal{L}} \mathbf{c}(u) (\mathbf{T}(u) - a_1 \mathbf{c}(u))^2 \\ &\quad + (1 - \mathbf{c}(u)) \mathbf{T}(u)^2 \\ &\quad + \tau_1 \sum_{\langle u,v \rangle} (\mathbf{T}(u) \\ &\quad - a_1 \mathbf{c}(u) - \mathbf{T}(v) \\ &\quad + a_1 \mathbf{c}(v))^2. \end{aligned} \quad (19)$$

In the above equation,  $c(u)$  is used as an indicator function. Accordingly, if its value is 1 (i.e.,  $u \in \mathcal{A}_1$ ), the term  $(1-c(u))\mathbf{T}(u)^2$  becomes zero, simplifying Eq. (19) to an expression that is equivalent to substituting  $\mathbf{n}(u)$  for  $\mathbf{T}(u) - a_1 c(u)$ . In Eq. (18), the activation level in  $\mathbf{T}(u)$  is eliminated, keeping only the noise component, as in the observation model proposed in (15).

Moreover, if  $c(u) = 0$  (i.e.,  $u \in \mathcal{A}_0$ ), the term  $c(u)(\mathbf{T}(u) - a_1 c(u))^2$  becomes zero and the term  $(\mathbf{T}(u) - a_1 c(u))$  in the second summation is simplified to  $\mathbf{T}(u)$ . This is equivalent to substituting  $\mathbf{n}(u)$  for  $\mathbf{T}(u)$  in Eq. (18), since  $\mathbf{T}(u)$  already corresponds to purely noise.

Eq. (19) may be rewritten as a quadratic function of a vector-valued field  $\mathbf{b}$  defined as  $\mathbf{b}_1(u) = c(u)$  and  $\mathbf{b}_0(u) = 1 - c(u)$ ,

$$U_{\mathbf{T}|\mathbf{b}}(\mathbf{b}) = \frac{1}{2}\gamma \sum_{u \in \mathcal{L}} \sum_{k \in \mathcal{K}} (\mathbf{T}(u) - a_k)^2 \mathbf{b}_k^2(u) + \tau_1 \sum_{\langle u,v \rangle} \sum_{i,j \in \mathcal{K}} (\mathbf{T}(u) - a_i - \mathbf{T}(v) + a_j)^2 \mathbf{b}_i(u) \mathbf{b}_j(v), \quad (20)$$

with  $a_0 = 0$  and:

$$\sum_{k \in \mathcal{K}} \mathbf{b}_k(u) = 1, \forall u \in \mathcal{L}, \quad (21)$$

$$\mathbf{b}_k(u) \in \{0,1\}, \forall u \in \mathcal{L}, k \in \mathcal{K}. \quad (22)$$

### Bayesian formulation of the hypothesis testing problem

For field  $\mathbf{b}$ , we propose the previous application of an MRF model <sup>[22] [23]</sup>. In order to introduce the prior constraint that the active regions are spatially cohesive,  $\mathbf{b}$  is modeled with Ising potentials, furnishing the following distribution:

$$P(\mathbf{b}) = \frac{1}{Z_{\mathbf{b}}} \exp(-U_{\mathbf{b}}(\mathbf{b})), \quad (23)$$

$$U_{\mathbf{b}}(\mathbf{b}) = \tau_2 \sum_{\langle u,v \rangle} \|\mathbf{b}(u) - \mathbf{b}(v)\|^2, \quad (24)$$

where  $\tau_2 \geq 0$  is a parameter that controls the granularity of field  $\mathbf{b}$ .

With this equation and the Gauss-Markov model (16) and (18) for noise, it is possible to estimate field  $\mathbf{b}$  by employing a Bayesian formulation, affording the posterior probability distribution:

$$P(\mathbf{b}|\mathbf{T}) \propto P(\mathbf{T}|\mathbf{b})P(\mathbf{b}), \quad (25)$$

where the likelihood is:

$$P(\mathbf{T}|\mathbf{b}) \propto \exp(-U_{\mathbf{T}|\mathbf{b}}(\mathbf{b})), \quad (26)$$

with  $U_{\mathbf{T}|\mathbf{b}}$  given by (20) and field  $\mathbf{b}$  satisfying (21)-(22). Finally, the posterior distribution can be written as:

$$P(\mathbf{b}|\mathbf{T}) \propto \exp(-U_{\mathbf{b}|\mathbf{T}}(\mathbf{b})), \quad (27)$$

$$U_{\mathbf{b}|\mathbf{T}}(\mathbf{b}) = U_{\mathbf{T}|\mathbf{b}}(\mathbf{b}) + U_{\mathbf{b}}(\mathbf{b}), \quad (28)$$

where  $U_{\mathbf{T}|\mathbf{b}}(\mathbf{b})$  and  $U_{\mathbf{b}}(\mathbf{b})$  are furnished by (20) and (24) respectively.

The MAP estimate for field  $\mathbf{b}$  is obtained by minimizing (28), subject to the constraints (21)-(22). This is a combinatorial optimization problem that is, in general, very difficult to solve. Several methods have been proposed, such as the iterated conditional modes (ICM) algorithm <sup>[24]</sup>, stochastic relaxation <sup>[25]</sup>, graph cuts procedure <sup>[26]</sup>, etc.

Here, because of the form of the cost function that includes the noise correlation term, we prefer option <sup>[22]</sup>, which is based on the relaxation of constraint (22). Hence, a new formulation is made:

$$\mathbf{b}_k(u) \geq 0, \forall k, u. \quad (29)$$

Dividing (28) by  $\gamma$  and utilizing  $\nu \stackrel{\text{def}}{=} \tau_1/\gamma$  and  $\lambda \stackrel{\text{def}}{=} \tau_2/\gamma$ , the functional is minimalized as:

$$U(\mathbf{b}; \nu, a_1, \lambda) = \frac{1}{2} \sum_{u \in \mathcal{L}} \sum_{k \in \mathcal{K}} (\mathbf{T}(u) - a_k)^2 \mathbf{b}_k^2(u) + \nu \sum_{(u,v)} \sum_{i,j \in \mathcal{K}} (\mathbf{T}(u) - a_i - \mathbf{T}(v) + a_j)^2 \mathbf{b}_i(u) \mathbf{b}_j(v) + \lambda \sum_{(u,v)} \|\mathbf{b}(u) - \mathbf{b}(v)\|^2. \quad (30)$$

If the noise has a mean of zero, then  $a_0 = 0$ . The resulting optimization problem is:

$$\text{Find } \mathbf{b}^*(\nu, a_1, \lambda) = \arg \min_{\mathbf{b}} U(\mathbf{b}; \nu, a_1, \lambda), \quad (31)$$

$$s. t: \sum_{k \in \mathcal{K}} \mathbf{b}_k(u) = 1, \forall u \in \mathcal{L}, \quad (32)$$

$$\mathbf{b}_k(u) \geq 0, \forall u \in \mathcal{L}, k \in \mathcal{K}. \quad (33)$$

This is a quadratic minimization problem, subject to linear constraints, which can be solved efficiently by employing a projected gradient descent method. Consequently, each  $\mathbf{b}(u)$  (in order to simplify the notation we remove the dependency of  $\nu, a_1, \lambda$ ) may now be interpreted as an approximation for the posterior marginal distribution of the indicator functions  $\mathbf{1}_{\mathcal{A}k(u)}$ .

To obtain the latter it is possible to set  $\mathbf{1}_{\mathcal{A}k(u)} = 1$  if  $\mathbf{b}_{k(u)} > \mathbf{b}_{j(u)}$  for all  $j \neq k$ . Thus, the estimation of the active region is:

$$\hat{\mathcal{A}} = \{ u \in \mathcal{L} \mid \mathbf{b}_1(u) > 0.5 \}. \quad (34)$$

### Parameter selection

A general method can now be introduced to allow the model (31)-(33) to be used for any type of noise. The parameters  $a_1, \nu, \lambda$  will be able to be automatically selected by controlling the false positive proportion while maximizing the performance of the method with respect to the TPR.

### Standardization of the noise field

The derivation of functional (31) is based on the observation model (15) with the Gauss-Markov model (16)-(18) for noise. However, the model is not always valid in practice, since the  $\mathbf{T}$  field may have a different distribution. The first step, therefore, is to generate a transformation capable of mapping the arbitrary distribution to a standard one. The proposed method is based on two properties:

- If  $x$  is a random variable and  $Q$  its corresponding *cumulative distribution function (CDF)*, then the distribution function for the random variable  $Q(x)$  is uniform [27] [28].
- If  $u$  is a uniform random variable and  $G$  the *CDF* of the normal distribution, then the distribution function for the random variable  $G^{-1}(u)$  is normal [29].

Combining both properties, it follows that for any random variable  $x$ , the random variable  $G^{-1}(Q(x))$  is normal. Consequently, the only requirement for transforming a random variable  $x$  into a normal variable is to know the corresponding *CDF*  $Q(x)$  or to estimate it by obtaining the empirical *CDF* (ECDF)  $\hat{Q}(x)$  from samples of the particular distribution.

Assuming that random field samples  $\mathbf{T}_0$  can be generated under  $H_0$ , it is possible to estimate the corresponding null distribution  $P_0(\cdot)$ . Given a field  $\mathbf{T}$  derived from the observations (e.g., the  $F$ -test for the generalized linear model (GLM) computed at each voxel), the sample can be mapped to a standard normal distribution  $\Phi$ :

$$\Phi(x) = \frac{1}{2} \left( 1 + \operatorname{erf} \left( \frac{x}{\sqrt{2}} \right) \right), \quad (35)$$

where  $\operatorname{erf}(y)$  denotes the error function [30], the probability that a random variable  $Z$  normally distributed with mean  $\mu = 0$  and variance  $\sigma = 1/2$  falls in the range  $[-y, y]$ . The field  $\hat{\mathbf{T}}$ , with a standard normal distribution, is afforded by the following transformation:

$$\hat{\mathbf{T}}(u) = \sqrt{2} \operatorname{erf}^{-1}(2P_0(\mathbf{T}(u)) - 1), \forall u \in \mathcal{L}. \quad (36)$$

### Hyper-parameter calibration

The hyper-parameters that control the behavior of the method are the spatial correlation parameter  $\nu$ , the minimum activation level  $a_1$ , and the regularization parameter  $\lambda$ . The general idea is to estimate  $\nu$  from the observations, and subsequently compute  $a_1, \lambda$  from the estimated parameter  $\nu$  and a parameter  $\epsilon$  representing the level of FPR control.

**Estimation of parameter  $\nu$ :** The parameter  $\nu = \tau_1/\gamma$  in (31) controls the noise spatial correlation and can be estimated by minimizing the negative logarithm of the pseudo-likelihood of samples of the field  $\mathbf{T}_0$  generated under  $H_0$  (i.e., samples of the noise field  $\mathbf{n}$ ).

The pseudo-likelihood is defined as the product of the conditional distributions for  $\mathbf{n}(u)$  at each pixel  $u$ , given the values at its neighboring fields<sup>[31]</sup>. Using Eqs. (17)-(18), the result is:

$$\begin{aligned} L(\gamma, \tau_1) &= -\log \prod_{u \in \mathcal{L}} P(\mathbf{n}(u) | \mathbf{n}(\nu), \nu \in \mathcal{N}_u, \gamma, \tau_1) \\ &= \left(\frac{\gamma}{2} + \tau_1 |\mathcal{N}_u|\right) p - 2\tau_1 q + \frac{\tau_1^2 r}{\frac{\gamma}{2} + \tau_1 |\mathcal{N}_u|} - \frac{|\mathcal{L}|}{2} \log \left(\frac{\gamma}{2} + \tau_1 |\mathcal{N}_u|\right) + t, \end{aligned} \quad (37)$$

where  $t$  is a constant,  $\mathcal{N}$  is the neighborhood of pixel  $u$  and:

$$p = \sum_{u \in \mathcal{L}} \mathbf{n}(u)^2 \quad (38)$$

$$q = \sum_{u \in \mathcal{L}} \mathbf{n}(u) \mathbf{s}(u) \quad (39)$$

$$r = \sum_{u \in \mathcal{L}} \mathbf{s}(u)^2 \quad (40)$$

$$\text{with } \mathbf{s}(u) = \sum_{v \in \mathcal{N}_u} \mathbf{n}(v). \quad (41)$$

The minimization of Eq. (37) yields a closed formula for the estimation of the parameters:

$$\tau_1 = \frac{q|\mathcal{L}|}{2(pr - q^2)}, \quad (42)$$

$$\gamma = 2 \left( \frac{r}{q} - |\mathcal{N}_u| \right) \tau_1, \quad (43)$$

$$\hat{\nu} = \frac{\tau_1}{\gamma}. \quad (44)$$

**Calibration of parameters  $a_1, \lambda$ :** For a given value  $\epsilon$  for FPR control and a fixed  $\nu = \hat{\nu}$  calculated with Eq. (44), the present proposal is to find the optimal parameter settings  $a_1^*, \lambda^*$  as the maximizers of the TPR, subject to  $FPR \leq \epsilon$ . However, the solution of such an optimization problem is very difficult to obtain because both TPR and FPR depend on the unknown region  $\mathcal{A}$ . To find an approximate solution, the following observations are made:

1. Instead of  $FPR \leq \epsilon$ , we use  $FPR_2 \leq \epsilon$ , Eq. (3), since the precise location of the boundary of the active region  $\mathcal{A}$  is uncertain (as aforementioned) and in some sense arbitrary, considering that activation generally has a gradual variation in the field.
2. According to our experimental work (see Fig. 2 and Experiment 1 below), the present method has the advantage that false positives do not extend, in a significant way, more than a couple of pixels away from this boundary. This is due to boundary effects close to the active region. For a given fixed  $a_1$  and  $\lambda$ , therefore, it is possible to estimate the constraint  $FPR_2 \leq \epsilon$  by  $FPR^0$  (i.e., the FPR computed in fields generated under  $H_0$ ), which is depicted by  $FPR^0(a_1, \lambda)$ .

3. The calculation can be further simplified based on the observation that TPR is an increasing function of FPR (i.e., the usual shape of the ROC curves). Consequently, for a fixed  $\lambda$ :

$$\hat{a}_1(\lambda) = \arg \max_{a_1} TPR(a_1, \lambda), \quad (45)$$

which is equivalent to finding  $a_1(\lambda)$ , such that  $FPR^0(a_1(\lambda), \lambda) = \epsilon$ . Given that a  $\hat{a}_1$  is obtained from fields produced under  $H_0$  and these fields are standardized as described above with the noise model (18), the values of  $a_1$  as a function of  $v, \lambda, \epsilon$  do not depend on the data. Hence, it is possible to pre-compute them based on fields generated by utilizing model (16) with  $U$  afforded by (18), being then the Gibbs sampler algorithm [25].

4. Since the TPR depends on the unknown  $\mathcal{A}$ , we propose the approximation of TPR for each value of  $\lambda$  by the average  $\overline{TPR}(\lambda)$ . The latter value results from running the method with the value  $\hat{a}_1(\lambda)$  for a  $\hat{a}_1$  over a finite set of values  $\hat{S}$ , which is a discretized version of the collection of activation values  $S$  in a continuous interval. We use a fixed synthetic active region (a circle):

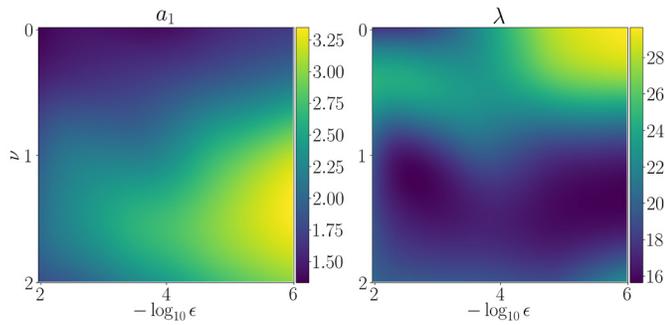
$$\begin{aligned} \overline{TPR}(a_1, \lambda; v, \epsilon) = & \\ \int_{a \in S} TPR(a, a_1, \lambda; v, \epsilon) P(a) da \approx & \quad (46) \\ \frac{1}{|\hat{S}|} \sum_a TPR(a, \hat{a}_1(\lambda; v, \epsilon), \lambda; v, \epsilon), & \end{aligned}$$

where  $P(a)$  is taken as the uniform distribution in the set  $S$ . With these simplifications, the parameter estimation algorithm simply consists of sweeping the plausible  $\lambda$  values in a given set  $\Lambda$  (a discretization of an interval  $[0, \lambda_{\max}]$ ), followed by finding, for each  $\lambda$ , the value  $\hat{a}_1(\lambda)$  (such that  $FPR(\hat{a}_1(\lambda), \lambda) = \epsilon$ ) and the corresponding  $\overline{TPR}(\lambda)$ , as explained above. The final  $\lambda^*$  is then found as the maximizer of  $\overline{TPR}(\lambda)$ , affording  $a_1^* = \hat{a}_1(\lambda^*)$ . This is summarized in Algorithm 1.

The optimal parameters  $a_1^*, \lambda^*$  depend on the data only through the estimated parameter  $v$  and the desired  $FPR^0$  control  $\epsilon$ . Thus, the optimal values may be pre-computed and stored in a table. When a new data set arrives, one only needs to standardize the noise, estimate  $v$ , read  $a_1^*, \lambda^*$  from the table for the desired  $FPR$  control, and minimize  $U(\mathbf{b}; v, a_1^*, \lambda^*)$  furnished by Eq. (30). The tables are represented as false color images in Figure 1.

The final algorithm for estimating the active region  $\hat{\mathcal{A}}$  for a given data set is summarized in Algorithm 2.

<b>Algorithm 1:</b> Calibration parameter algorithm (CPA)	
<b>function</b> CPA( $v, \epsilon$ )	
<b>1 Input</b>	Estimated value of $v$ from (44); desired control $\epsilon$ for the FPR; search interval $\Lambda$ for $\lambda$ .
<b>Output</b>	Estimated hyperparameter values $a_1^*, \lambda^*$
<b>2 Begin</b>	
<b>3 For all</b> $\lambda \in \Lambda$ <b>do</b>	
<b>4</b>	Compute $\hat{a}_1(\lambda; v, \epsilon)$ that solves $FPR(a_1, \lambda; v) = \epsilon$ ;
<b>5</b>	Compute $\overline{TPR}(\hat{a}_1(\lambda; v, \epsilon), \lambda; v, \epsilon)$ by using (46);
<b>6 End</b>	
<b>7</b>	Compute $\lambda^* = \arg \max_{\lambda \in \Lambda} \overline{TPR}(\hat{a}_1(\lambda; v, \epsilon), \lambda; v, \epsilon)$
<b>8</b>	Compute $a_1^* = \hat{a}_1(\lambda^*(v, \epsilon); v, \epsilon)$ ;
<b>9 Return</b> $a_1^*, \lambda^*$	
<b>10 End</b>	
<b>Algorithm 2:</b> Regularized hypothesis testing (RHT) algorithm	
<b>function</b> RHT( $\mathbf{T}, \hat{\epsilon}, a_1^*(v, \epsilon), \lambda^*(v, \epsilon)$ )	
<b>1 Input</b>	Observed field $\mathbf{T}$ , parameters $a_1^*(v, \epsilon), \lambda^*(v, \epsilon)$ computed with Algorithm 1 and the desired control for the FPR
<b>Output</b>	Estimated active region $\hat{\mathcal{A}}$
<b>2 Begin</b>	
<b>3</b>	Compute $\hat{\mathbf{T}}$ with (36);
<b>4</b>	Compute $\hat{v}$ with (44) using the field $\hat{\mathbf{T}}$ ;
<b>5</b>	Compute $\hat{a}_1 = a_1^*(\hat{v}, \hat{\epsilon})$ by interpolating $a_1^*(v, \epsilon)$ from a pre-computed table;
<b>6</b>	Compute $\hat{\lambda} = \lambda^*(\hat{v}, \hat{\epsilon})$ by interpolating $\lambda^*(v, \epsilon)$ from a pre-computed table;
<b>7</b>	Compute $b^*(\hat{v}, \hat{a}_1, \hat{\lambda})$ by solving (31)-(33);
<b>8</b>	Compute $\hat{\mathcal{A}}$ with (34);
<b>9 Return</b> $\hat{\mathcal{A}}$	
<b>10 End</b>	



**FIGURE 1. Estimation of parameters  $\alpha_1, \lambda$  as functions depending on  $(\nu, -\log_{10} \epsilon)$  for  $\nu \in [0, 2]$  and  $\epsilon \in [10^6, 10^{-2}]$ .**

## MATERIALS AND METHODS

### Data description

To study the behavior of the present method, we include various experiments based on both synthetic and real data.

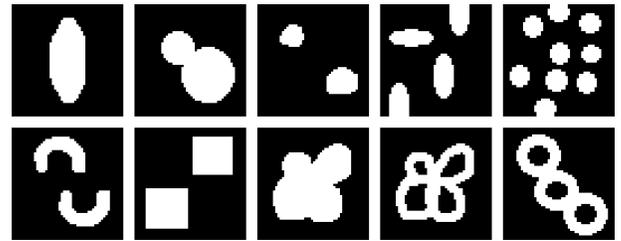
**Synthetic data:** The synthetic data was generated dynamically and consisted of two components. Firstly,  $\mathcal{S}_0 = \{n_1, n_2, \dots, n_{40}\}$  is a set of noise fields of a regular lattice  $\mathcal{L}$  of  $50 \times 50$  pixels, without any activation region. That is, the images were produced under  $H_0$ , using Eqs. (16) and (18) with  $n(u)$  as random independent variables showing standard Gaussian distribution. Parameter  $\gamma = 1$  and  $\nu$  were to be specified in each experiment. Secondly,  $\mathcal{S}_1 = \{c_1, c_2, \dots, c_{40}\}$  consists of 40 binary labeled fields of a regular lattice of  $50 \times 50$  pixels, representing indicator functions for activation regions of different shapes (see Figure 2). Then, the simulated observed fields are generated by the following model:

$$\hat{a}_1(\lambda) = \arg \max_{\alpha_1} TPR(\alpha_1, \lambda), \quad (47)$$

where  $a$  denotes the activation level and its value is specified in each experiment.

**Real data:** Experiments with real data were based on the auditory dataset [32]. The data corresponded to 96 volumes of a single subject (each volume composed of

$64 \times 64 \times 64$  voxels of  $1 \times 1 \times 3$  mm), which were acquired in blocks of 6 volumes. Since the repetition time between scanning was set to 7 seconds, there were a total of 16 blocks of 42 seconds (although due to the effects related to T1, the first two blocks were discarded). The sequence of volumes alternated between blocks of rest and stimulation, starting with rest. Auditory stimulation consisted of two-syllable words presented binaurally at a rate of 60 per minute.



**FIGURE 2. Dataset: Examples of synthetic active regions.**

### Localization of false positives for the RHT algorithm

This experiment was designed to test the assumption that in the proposed method the false positive errors are concentrated close to the boundary of the active region. Consequently,  $FPR_2$  can be well approximated by  $FPR_0$  (i.e., FPR computed over images produced under  $H_0$ ).

A total of 1000 independent runs were conducted for the procedure. Briefly, set  $\mathcal{S}_0$  was generated with parameter  $\nu = 0.75$ , a value estimated from fMRI images by utilizing Eq. (44). Fields  $\mathbf{T}_1, \mathbf{T}_2, \dots, \mathbf{T}_{40}$  were obtained by using model (47), sets  $\mathcal{S}_0$  and  $\mathcal{S}_1$ , and randomly selected activation level  $\alpha$  in the interval [2] [4].

Algorithm 2 was applied for levels of FPR control  $\epsilon \in \{0.001, 0.0001, 0.00001, 0.000001\}$  with the optimally calibrated parameters, computing the average value of  $FPR_2$  for the set  $\mathcal{S}_1$  and  $FPR$  for the set  $\mathcal{S}_0$ . The results are shown in Table 1. As can be appreciated, by calibrating the parameters of the method to control  $FPR_0$ , the appropriate control over  $FPR_2$  is also achieved.

## Performance of the method

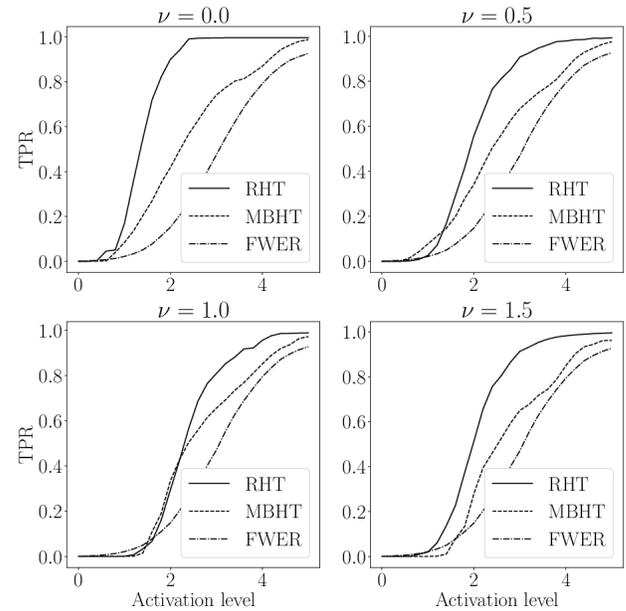
The first set of the following experiments was designed to make a comparison of RHT to FWER [8] and MBHT [12], the latter two being the state-of-the-art methods that take the spatial expanse of the active region into account. Accordingly, the set  $S_0$  was produced with parameter  $\nu \in \{0, 0.5, 1, 1.5\}$ . A total of 1000 runs were performed, randomly selecting the active regions  $\mathcal{A}$  from  $\mathcal{S}_1$  with an activation level  $a \in \{0.0, 0.25, 0.5, \dots, 5\}$ . The average TPR was computed. The RHT method was carried out by employing Algorithm 2 and a level of false positive control of  $\hat{\epsilon} = 0.000001$ .

Based on the results from each method, RHT proved capable of providing better TPR values than the other two algorithms for most activation levels (Figure 3). The improvement is likely due to the consideration in the new model of the spatial cohesion of the activation regions (controlled by the regularization parameter  $\lambda$ ) as well as the spatial correlation in the noise field (controlled by the parameter  $\nu$ ). Contrarily, the rest of the algorithms assume that these two components of statistic  $T$  are formed by independent variables.

## Experiments with fMRI data

In the second set of experiments, Algorithm 2 of the proposed method was applied to the real fMRI data described at the beginning of this section. RHT was not applied directly to the original data, but rather to a field  $T$  (an  $F$ -test field computed from the data). The first step was to standardize the field in order to obtain  $\hat{T}$  with Eq. (36), which is the input of the segmentation algorithm. Hence, it was necessary to calculate the ECDF from the data. Here after, some details about the aforementioned steps are explained.

**Data pre-processing.** The aim of the pre-processing was to remove artifacts in the data as well as to prepare the data to maximize the statistical analysis. Here we use spatial pre-processing provided in the script `auditory_spm12_batch.m`, which implies realignment,



**FIGURE 3.** Performance comparison of RHT with the punctual FWER and MBHT methods for different noise spatial correlation  $\nu$  and  $\epsilon = 0.000001$ .

co-registration, segmentation and normalization. Although the original script (available online at <http://www.fil.ion.ucl.ac.uk/spm/data/auditory/>) includes a smoothing step to ensure that some assumptions about noise distribution are fulfilled [11] [18], RHT omits this step because it is capable of handling different noise distributions. Actually, the inclusion of the step would not be beneficial. The data for these calculations was processed on SPM software version 12 (available at <http://www.fil.ion.ucl.ac.uk/spm/>) and MATLAB 2018a. A slice of the pre-processed data was selected to perform the following experiments.

**F-test field.** After the pre-processing stage, the statistical analysis was carried out to determine the active voxels that correspond to a given stimulus. To obtain the active regions, a voxel-wise analysis is typically conducted by fitting models to a single voxel time course. The data at each voxel is modeled in a univariate way with a linear model:

$$y_t = \beta_0 + \beta_1 x_t + \epsilon_t, \quad (48)$$

**TABLE 1. Experiment of the FPR control at different levels, utilizing a synthetic dataset. First column, level of FPR control; second column, average FPR for images generated under  $H_0$ ; third column, average  $FPR_2$  for synthetic active regions.**

$\epsilon$	FPR <sup>0</sup>	FPR <sup>2</sup>
0.01	0.0042504	0.0051335
0.001	0.0001340	0.0001714
0.0001	0.0000436	0.0000436
0.00001	0.0000044	0.0000050
0.000001	0.0000004	0.0000004

where  $y_t$ , the dependent variable, is a vector formed by the intensity values at each time point.  $\beta_0$  and  $\beta_1$  are the intercept and the slope of the linear model, respectively. Meanwhile,  $\epsilon_t$  is the error term in the model fitting, which captures factors other than  $x_t$ , such as signal noise, capable of affecting  $y_t$ . The explanatory variable  $x_t$  corresponds to the model of neural activity. It is also a vector comprised of entries depicting a real value at each time point:

$$x_t = d_t * h_t \quad (49)$$

where  $h_t$  stands for the hemodynamic response function and  $d_t \in \{0,1\}$  is an impulse train that indicates whether the stimulus was present at time  $t$ . Then, the neural activity is modeled as a convolution,\* in which the *hemodynamic response function* acts as a filter.

The  $F$ -test represents the ratio between the variance described in a reduced model  $y_t = \beta_0 + \epsilon_t$  (without any additional effect) and the full model (48)-(49) that includes the effect of interest.

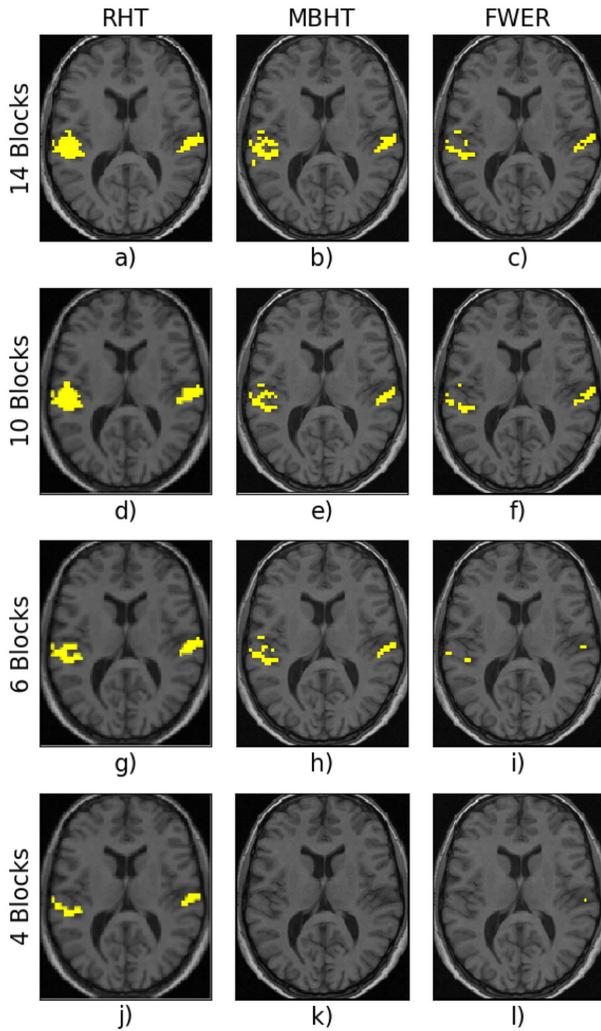
Finally, the  $F$ -test was computed for every voxel in the volume. The resulting field was the input for the RHT algorithm, calculated by using the script `auditory_spm12_batch.m` with the default parameters.

**Null distribution.** Before the segmentation step of the RHT algorithm, it was necessary to normalize the  $F$ -test field and thus to estimate the null distribution. More specifically, a sample of the  $F$ -test was obtained under  $H_0$ , allowing for the computation of the corresponding ECDF. This was carried out by permuting the order of the stimulus labels  $\mathbf{d}(t)$  for the volumes (see [33] for more details), and by calculating the  $F$ -test field for each permutation, as explained in the previous section. After completion of these procedures, it was possible to apply Eq. (36) to transform the original  $F$ -test field (i.e., the original order of the labels  $\mathbf{d}(t)$ , without permutation) to one that follows a standard normal distribution. Finally, for the  $\hat{T}$  fields generated under  $H_0$ , the value of  $\nu$  was estimated by utilizing Eq. (44), finding  $\nu = 0.75$ .

### RHT algorithm robustness with respect to SNR

In order to investigate the stability of the present method, the algorithm was tested by modifying the SNR in the data from which the activation region would be established. Accordingly, blocks of observations were eliminated from the full experiment. As aforementioned, the first two of the 16 original blocks were eliminated due to effects related to T1. Hence, 14 blocks (84 volumes) were taken initially to perform the procedure described earlier in this section to identify the activation regions. Subsequently, the number of blocks was reduced by two, taking 12 blocks (72 volumes) and performing the procedure again to determine the activation regions, and so on until reaching 4 blocks.

In each case, a tolerance for false positives to  $\epsilon = 0.0001$  was established and the results of RHT were compared to those obtained with MBHT and FWER using the same number of blocks. It can be verified by visual inspection (Figure 4) that the three methods—RHT, MBHT and FWER—detected activation regions corresponding to the primary auditory cortex, located at the upper sides of the temporal lobes, specifically on the transverse temporal gyri [34] [35].



**FIGURE 4. Performance comparison of the RHT, MBHT and FWER by modifying the SNR in the data through the elimination of blocks.**

The MBHT and RHT methods afforded better performance and robustness for the reduction of information in most cases. MBHT and FWER displayed less accuracy when reducing the signal information for  $\epsilon = 0.00001$ . While FWER exhibited difficulties in the identification of activation regions with 6 and 4 blocks (barely finding any region), RHT and MBHT gave better performance. However, when the number of blocks was decreased to only 4, MBHT was not able to detect any activation region, while RHT still had a proficient outcome. RHT outperformed the other models two by successfully recovering both regions.

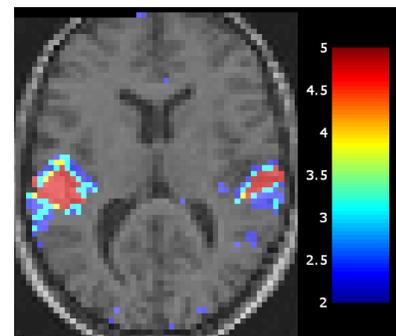
**Degree of false positive control.** To avoid having to specify a particular value for  $\epsilon$ , it is possible to estimate  $\mathcal{A}$  for a set  $\mathcal{S}$  of  $\epsilon$  values and produce a map in which the degree of false positive control ( $\log \epsilon$  for each  $\hat{\mathcal{A}}(\epsilon) = \text{RHT}(\mathbf{T}, \hat{\epsilon}, a_1^*(v, \epsilon), \lambda^*(v, \epsilon))$  is color coded. The result is very similar to the p-value maps that are created for the classic PW method. Specifically, we define the degree of false positive control at site  $u$  as:

$$\max_{\epsilon \in \mathcal{S}} [(-\log \epsilon) \mathbf{1}_{\hat{\mathcal{A}}(\epsilon)}(u)], \quad (50)$$

where  $\mathbf{1}_{\hat{\mathcal{A}}(\epsilon)}(u)$  is the indicator function for the set  $\hat{\mathcal{A}}(\epsilon)$ . An example of this type of map is shown in Figure 5, with  $\mathcal{S} = \{0.01, 0.001, 0.0001, 0.00001\}$ . The map portrays important differences between the first and second levels, but in the last levels the detected regions are more similar to each other. The slight variations exist only at the border of the active region.

## RESULTS AND DISCUSSION

We herein describe a new method, RHT, for detecting active regions in random fields. The focus is on applications for neuroimaging. With the present method, the expected TPR is maximized while the false positives are kept under control by specifying an upper bound  $\epsilon$  on  $FPR^0$  (the FPR under  $H_0$ ). By making  $\epsilon$  small enough, there is an effective correction for multiple hypotheses since the total number of false positives in the entire field is controlled. We demonstrated experimentally that most of the false positives produced by



**FIGURE 5. Degree of false positive control over fMRI data described in the text.**

RHT are confined to the vicinity of the boundary of the active region. Thus,  $\epsilon$  also bounds the FPR in the data outside of this boundary (i.e., the  $FPR_2$ ).

## CONCLUSIONS

The main contributions of the present model are the following:

1. A Bayesian formulation of the hypothesis testing problem in random fields was reduced to an image or volume segmentation problem, for which the maximum a posteriori estimate could be calculated.
2. A new Markovian random field model for correlated noise was implemented, from which the appropriate prior distribution could be computed.
3. A method for estimating the hyper-parameters of the model was conceived, involving two main factors: a) the application of a closed formula for the noise correlation parameter  $\nu$  based on the maximization of the pseudo-likelihood of the data, and b) a pre-calculated lookup table (independent of the data) for the  $\lambda$  and  $a_1$  parameters. This method makes the whole procedure computationally efficient, since the only thing needed for its application is a way of generating sample images from the null distribution. Such samples can be obtained, for example, by using permutation procedures.
4. To avoid having to specify a particular value for the  $\epsilon$  parameter, we demonstrated how to present a family of solutions for different values of  $\epsilon$  in a single image (the DFPC map), similar to the classic p-value maps.
5. The performance of the method was validated with synthetic and real data (fMRI images). In both cases, RHT provided an improvement in the TPR (while maintaining the FPR under control) compared to the competitive state-of-the-art methods (MBHT and FWER). For the fMRI data, RHT displayed the best sensitivity, which was particularly high for low SNR.

For simplicity, in the current analysis we focused on two-dimensional data. However, it is possible to directly extend the method to 3D simply by considering an extended neighborhood (e.g., 6 or 26 neighbors for each voxel) in the prior MRF models for the active region and the noise, at the expense of an increased computational complexity.

Although the example application here corresponds to fMRI, the RHT method may be applied to any situation involving the testing of a field of local hypotheses, such as the ones that are common in neuroimaging, remote sensing, and so on.

## ABBREVIATIONS

CDF, cumulative distribution function  
 ECDF, empirical cumulative distribution function  
 FDR, false discovery rate  
 FPR, false positive rate  
 fMRI, functional magnetic resonance imaging  
 FWER, family-wise error rate  
 GMRF, Gaussian Markov random fields  
 $H_0$ , null hypothesis  
 MBAT, morphology-based hypothesis testing  
 MAP, maximum a posterior probability  
 MRF, Markovian random field  
 PW, pointwise method  
 RHT, regularized hypothesis testing  
 ROC, receiver operating characteristic  
 SNR, signal-to-noise ratio  
 TPR, true positive rate

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## AUTHOR CONTRIBUTIONS STATEMENT

O.D. and J.M. conceived the method and the experiments, the latter conducted by D.A. O.D., D.A. and J.M. analyzed the results. All authors reviewed and approved the final version of the manuscript.

## REFERENCES

- [1] Cole MW, Ito T, Bassett DS, Schultz DH. Activity flow over resting-state networks shapes cognitive task activations. *Nature Neuroscience*. 2016 October; 19(0): p. 1718-1726, doi: [10.1038/nn.4406](https://doi.org/10.1038/nn.4406).
- [2] Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafò MR, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nature Reviews Neuroscience*. 2017 January; 18(0): p. 115-126, doi: [10.1038/nrn.2016.167](https://doi.org/10.1038/nrn.2016.167).
- [3] Mejia A, Yue YR, Bolin D, Lindren F, Lindquist MA. A Bayesian General Linear Modeling Approach to Cortical Surface fMRI Data Analysis. *Journal of the American Statistical Association*. 2019 April; 0(0): p. 1-20, doi: [10.1080/01621459.2019.1611582](https://doi.org/10.1080/01621459.2019.1611582).
- [4] Flores-Leal M, Sacristán-Rock E, Jiménez-Ángeles L, Leehan JA. Primed low frequency transcranial magnetic stimulation effects on smoking cue-induced craving. *Revista mexicana de ingeniería biomédica*. 2016 April; 37(1): p. 39-48, doi: [10.17488/RMIB.37.1.3](https://doi.org/10.17488/RMIB.37.1.3).
- [5] Acosta-Franco JA, Saiffe-Farías AF, Gómez-Velázquez FR, González-Garrido AA, Romo-Vázquez RC. Activación Hemisférica Cerebral en Adultos Jóvenes Mientras Ejecutan Tareas Ortográficas Utilizando fMRI. *Revista Mexicana de Ingeniería Biomédica*. 2019 August; 40(2): p. 1-10, doi: [10.17488/RMIB.40.2.5](https://doi.org/10.17488/RMIB.40.2.5).
- [6] Lindquist MA, Mejia A. Zen and the Art of Multiple Comparisons. *Psychosomatic medicine*. 2015 February; 77(2): p. 114-125, doi: [10.1097/PSY.0000000000000148](https://doi.org/10.1097/PSY.0000000000000148).
- [7] Woo CW, Krishnan A, Wager TD, Woo, C.-W., Krishnan, A., & Wager, T. D. (2014). Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. *NeuroImage*. 2013 December; 91(0): p. 412-419, doi: [10.1016/j.neuroimage.2013.12.058](https://doi.org/10.1016/j.neuroimage.2013.12.058).
- [8] Abdi H. The Bonferroni and Sidak corrections for multiple comparisons. In Salkind NJ, editor. *Encyclopedia of Measurement and Statistics*. Thousand Oaks, CA, USA: Sage Publications; 2007. p. 103-107, doi: [10.4135/9781412952644](https://doi.org/10.4135/9781412952644).
- [9] Hayasaka S, Nichols TE. Validating cluster size inference: random field and permutation methods. *NeuroImage*. 2003 December; 20(4): p. 2343-2356, doi: [10.1016/j.neuroimage.2003.08.003](https://doi.org/10.1016/j.neuroimage.2003.08.003).
- [10] Hagler DJ, Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *NeuroImage*. 2006 December; 33(4): p. 1093-1103, doi: [10.1016/j.neuroimage.2006.07.036](https://doi.org/10.1016/j.neuroimage.2006.07.036).
- [11] Eklund A, Nichols TE, Knutsson H. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences*. 2016 July; 113(28): p. 7900-7905, doi: [10.1073/pnas.1602413113](https://doi.org/10.1073/pnas.1602413113).
- [12] Marroquin JL, Biscay RJ, Ruiz-Correa S, Alba A, Ramirez R, Armony JL. Morphology-based hypothesis testing in discrete random fields: A non-parametric method to address the multiple-comparison problem in neuroimaging. *NeuroImage*. 2011 February; 56(4): p. 1954-1967, doi: [10.1016/j.neuroimage.2011.09.051](https://doi.org/10.1016/j.neuroimage.2011.09.051).
- [13] Swets JA. *Signal detection theory and ROC analysis in psychology and diagnostics: Collected papers*. 1st ed. Press P, editor. New York, USA.: Psychology Press; 2014, doi: [10.4324/9781315806167](https://doi.org/10.4324/9781315806167).
- [14] Hochberg Y, Tamhane AC. *Distribution-Free and Robust Procedures*. 1st ed. Shube B, editor. New York, USA.: Wiley Online Library; 1987, doi: [10.1002/9780470316672](https://doi.org/10.1002/9780470316672).
- [15] Pantazis D. General Linear Modeling of Magnetoencephalography Data. In Bronzino JD, Peterson DR, editors. *Biomedical Signals, Imaging, and Informatics*. Boca Raton, Florida, USA.: CRC Press; 2014. p. 33-350, doi: [10.1201/b15468](https://doi.org/10.1201/b15468).
- [16] Benjamini Y. Discovering the false discovery rate. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. 2010 August; 72(4): p. 405-416, doi: [10.1111/j.1467-9868.2010.00746.x](https://doi.org/10.1111/j.1467-9868.2010.00746.x).
- [17] Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I. Controlling the false discovery rate in behavior genetics research. *Behavioural brain research*. 2001 November; 125(1-2): p. 279-284, doi: [10.1016/S0166-4328\(01\)00297-2](https://doi.org/10.1016/S0166-4328(01)00297-2).
- [18] Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE, Penny WD. *Statistical parametric mapping: the analysis of functional brain images*. 1st ed. Penny W, editor. London, UK.: Academic press; 2011, doi: [10.1016/B978-0-12-372560-8.X5000-1](https://doi.org/10.1016/B978-0-12-372560-8.X5000-1).
- [19] Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human brain mapping*. 2002 January; 15(1): p. 1-25, doi: [10.1002/hbm.1058](https://doi.org/10.1002/hbm.1058).
- [20] Welvaert M, Rosseel Y. On the definition of signal-to-noise ratio and contrast-to-noise ratio for fMRI data. *PloS one*. 2013 November; 8(11): p. 1-10, doi: [10.1371/journal.pone.0077089](https://doi.org/10.1371/journal.pone.0077089).
- [21] Zhang H, Nichols TE, Johnson TD. Cluster mass inference via random field theory. *NeuroImage*. 2009 January; 44(1): p. 51-61, doi: [10.1016/j.neuroimage.2008.08.017](https://doi.org/10.1016/j.neuroimage.2008.08.017).
- [22] Rivera M, Ocegueda O, Marroquin JL. Entropy-controlled quadratic Markov measure field models for efficient image segmentation. *IEEE Transactions on Image Processing*. 2007 December; 16(12): p. 3047-3057, doi: [10.1109/TIP.2007.909384](https://doi.org/10.1109/TIP.2007.909384).
- [23] Dalmau O, Rivera M. Beta-Measure for Probabilistic Segmentation. In *Advances in Artificial Intelligence: 9th Mexican International Conference on Artificial Intelligence, MICAI 2010*, Pachuca, Mexico, November 8-13, 2010, Proceedings, Part I; 2010; Berlin, Heidelberg: Springer Berlin Heidelberg. p. 312-324, doi: [10.1007/978-3-642-16761-4\\_28](https://doi.org/10.1007/978-3-642-16761-4_28).
- [24] Besag J. On the statistical analysis of dirty pictures. *Journal of the Royal Statistical Society B*. 1986 January; 48(3): p. 48-259, doi: [10.1080/02664769300000059](https://doi.org/10.1080/02664769300000059).
- [25] Geman S, Geman D. Stochastic Relaxation, Gibbs Distributions, and the Bayesian Restoration of Images. *IEEE Transactions on Pattern Analysis and Machine Intelligence*. 1984 November; PAMI-6(6): p. 721-741, doi: [10.1109/TPAMI.1984.4767596](https://doi.org/10.1109/TPAMI.1984.4767596).
- [26] Boykov Y, Veksler O, Zabih R. Fast Approximate Energy Minimization via Graph Cuts. *IEEE Trans. Pattern Anal. Mach. Intell.* 2001 November; 23(11): p. 1222-1239, doi: [10.1109/34.969114](https://doi.org/10.1109/34.969114).
- [27] Wu YL, Agrawal D, Abbadi AE. Applying the golden rule of sampling for query estimation. *ACM SIGMOD Record*. 2001 May; 10(2): p. 449-460, doi: [10.1145/376284.375724](https://doi.org/10.1145/376284.375724).

- [28] Devroye L. General Principles in Random Variate Generation. In Springer-Verlag, editor. Nonuniform random variate generation. New York, New York 10010, U.S.A: Elsevier; 2006. p. 27-36, [doi: 10.1016/S0927-0507\(06\)13004-2](https://doi.org/10.1016/S0927-0507(06)13004-2).
- [29] Drew JH, Evans DL, Glen AG, Leemis LM. Transformations of random variables. In Grassmann WK, editor. Computational Probability. Boston, MA, USA: Springer; 2017. p. 47-46, [doi: 10.1007/978-0-387-74676-0](https://doi.org/10.1007/978-0-387-74676-0).
- [30] Oldham KB, Myland JC, Spanier J. The Error Function erf (x) and Its Complement erfc (x). In Science S, editor. An Atlas of Functions. New York, USA: Springer; 2008. p. 405-415, [doi: 10.1007/978-0-387-48807-3\\_41](https://doi.org/10.1007/978-0-387-48807-3_41).
- [31] Besag J. Statistical Analysis of Non-Lattice Data. Journal of the Royal Statistical Society. Series D (The Statistician). 1975 January; 24(3): p. 179-195, [doi: 10.2307/2987782](https://doi.org/10.2307/2987782).
- [32] Friston K. Single subject epoch (block) auditory fMRI activation data [Internet]. 1999. Available from: <http://www.fil.ion.ucl.ac.uk/spm/data/auditory>.
- [33] Raz J, Zheng H, Ombao H, Turetsky B. Statistical tests for fMRI based on experimental randomization. NeuroImage. 2003 June; 19(2): p. 226-232, [doi: 10.1016/s1053-8119\(03\)00115-0](https://doi.org/10.1016/s1053-8119(03)00115-0).
- [34] Amunts K, Morosan P, Hilbig H, Zilles K. Chapter 36 - Auditory System. In Mai JK, Paxinos G, editors. The Human Nervous System (Third Edition). New York, USA.: Academic Press; 2012. p. 1270-1300, [doi: 10.1016/C2009-0-02721-4](https://doi.org/10.1016/C2009-0-02721-4).
- [35] Bizley J. Audition. In Conn PM, editor. Conn's Translational Neuroscience. New York, USA: Elsevier; 2017. p. 579-598, [doi: 10.1016/B978-0-12-802381-5.00042-7](https://doi.org/10.1016/B978-0-12-802381-5.00042-7).

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## A Socio-technical Approach to Evaluating an Electronic Medical Record System implemented in the Public Health Services of Aguascalientes

### Una Aproximación Socio-técnica a la Evaluación de un Expediente Médico Electrónico implementado en Servicios de Salud Públicos de Aguascalientes

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#### ABSTRACT

The objective of this study was to explore a strategy for evaluating an Electronic Medical Record (EMR) system implemented in the public health services of Aguascalientes, Mexico. A questionnaire based on DeLone and McLean's Model of Information Systems Success (MISS) was adapted to Spanish and applied with 62 primary care physicians working in health centers of the *Instituto de Servicios de Salud del Estado de Aguascalientes* (ISSEA or the State of Aguascalientes Institute for Health Services). Opportunities for improving EMR systems were also explored from the informants' perspectives. Additionally, the relationships between MISS components were analyzed using Structural Equations Modeling (SEM). Some MISS components and particular items (service quality and overall satisfaction) presented low averages, reflecting opportunities for improving the development and implementation of EMR, such as the need to continuously update information pertaining to diagnostic and medicine catalogs and develop systems that are interoperable between the second and third levels of care. In conclusion, the present study contributes generating evidence on the use of the MISS to evaluating EMR systems in public health services of Mexico. More evidence should be generated in this field in order to promote the continuous improvement of these information systems.

**KEYWORDS:** Information science; Information technology management; Medical informatics; Implementation science; Primary health care

## RESUMEN

El objetivo de este estudio fue explorar una estrategia para la evaluación de un Expediente Clínico Electrónico (ECE) implementado en servicios de salud públicos de Aguascalientes, México. Se adaptó al español un cuestionario basado en el Modelo de Éxito de Sistemas de Información (MISS) de DeLone y McLean y se aplicó a 62 médicos de atención primaria que trabajan en centros de salud del Instituto de Servicios de Salud del Estado de Aguascalientes (ISSEA). Se exploraron también las oportunidades de mejora del ECE desde la perspectiva de los informantes. Además, se analizaron las relaciones entre los componentes del MISS mediante el modelado de ecuaciones estructurales (SEM). Algunos componentes del MISS e ítems particulares mostraron promedios bajos (p.ej., calidad del servicio y satisfacción) que reflejan algunas oportunidades de mejora en el desarrollo e implementación del ECE, como la necesidad de una actualización continua de la información sobre diagnósticos y catálogos de medicamentos; y el desarrollo de sistemas de interoperabilidad con el segundo y tercer nivel de atención. En conclusión, el presente estudio contribuye en la generación de evidencia sobre el uso del MISS para evaluar los sistemas de EMR en servicios de salud públicos de México. Se debe generar más evidencia en este campo para promover la mejora continua de estos sistemas de información.

**PALABRAS CLAVE:** Ciencia de la información, Administración de las Tecnologías de la Información; Informática médica; Ciencia de la implementación; Atención primaria de salud

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## INTRODUCTION

Information and Communication Technologies (ICT) are an important resource for improving the performance of health systems. The applications of ICT in health are closely related to the concept of electronic health (e-Health), which is defined as “the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research” [1]. A similar concept, under the term digital health, has also been recently introduced [2] [3].

The application of ICT in the areas of health surveillance, monitoring, prevention, promotion and care, at various levels or fields of application, has evolved into the concepts of e-Health and digital health [4].

As the principal components of e-health are the following: health information systems (HIS) supported by ICT (public health informatics, clinical informatics, and consumer health informatics); Electronic Medical Records (EMR); Electronic Health Records (EHR); Picture Archiving and Communication Systems (PACS); Clinical Decision Support Systems (CDSS); remote care systems (telehealth and telemedicine); and, mobile systems (mobile health or *m-Health*). It should be noted that the eHealth innovations have been continually growing [5] [6] [7] [8] [9].

Various studies and systematic reviews have found evidence on the effectiveness and efficiency of the components of eHealth [10] [11] [12] [13], on the basis of which, global and regional organizations have issued diagnostics, policies, and recommendations for improving the implementation of ICT in the health systems of developing and developed countries [3] [14] [15] [16] [17] [18] [19] [20] [21]. To this end, various frameworks and recommendations have been developed from different disciplinary perspectives [22] [23] [24] [25] [26] [27].

In order to discuss eHealth in Mexico, it is essential to first describe the country’s *Sistema Nacional de Salud* (SNS or National Health System), which is characterized by its fragmentation into two large public and private sectors. The public sector is subdivided into health systems for people with formal employment and their direct family members (essentially a social security scheme) and health systems for people without formal employment. The social security system is made up the *Instituto Mexicano del Seguro Social* (IMSS or Mexican Social Security Institute), which comprised 39.2% of the sector in 2015; the *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado* (ISSSTE or Social Security and Services Institute for State Workers), which comprised 7.7% of the sector; and the health services used by the armed forces (*Secretaría de la Defensa Nacional*, SEDENA or Ministry of Defense, and *Secretaría de Marina*, SEMAR or Ministry of Navy) and employees of *Petróleos Mexicanos* (Pemex), which are provided by their respective institutions and comprised 1.2%. Health services for people without formal employment are mainly provided by the *Secretaría de Salud* (SSA or Ministry of Health) through the *Servicios Estatales de Salud* (SESA or State Health Services), which comprised 49.9% of the sector, although it is currently undergoing a process of incorporation into the newly-formed *Instituto de Salud para el Bienestar* (INSABI or Institute of Health for Welfare). There are also some special programs within the public sector, such as the *IMSS-Bienestar* (IMSS-Welfare) and the *Sistema Nacional para el Desarrollo Integral de la Familia* (DIF Nacional or National System for Integral Family Development) programs, that aim to provide health-care to vulnerable populations. Finally, the private sector comprises a multiplicity of service providers for people with the ability to pay for healthcare [28] [29] [30].

Recent federal administrations have pursued policies promoting the adoption and implementation of ICT, particularly in the public health sector. The last such policy was the *Estrategia Digital Nacional* (EDN or

National Digital Strategy) [31]. However, individual and organizational factors have limited the adoption and implementation of ICT, such as the persistently fragmented structure of the public health system.

Research on the adoption and implementation of ICT in the public health system in Mexico is scarce, which impedes a broad understanding of the problems faced by those making the decisions in this policy area. However, some general overviews have been published [14] [32] [33] [34], as well as some studies related to particular eHealth components, such as telemedicine [35] and mHealth [36] [37], and initiatives undertaken by private institutions [38] [39] [40]. Regarding EMR systems, some studies have analyzed the planning, adoption, and its implementation in public health institutions [32] [41] [42], focusing on identifying the factors that enable or hinder the success of this implementation. Some of these factors are related to technology (i.e., problems with diagnostic catalogs), the user (i.e., the age of some of the physicians providing primary care), and the organization itself (i.e., a lack of training or quality in its provision).

While the afore mentioned studies have focused principally on exploring the advances in and barriers to the implementation of EMR systems, they have not applied models or frameworks taken from behavioral sciences or social psychology [43] [44] as a guide. In this sense, some socio-technical frameworks have been developed to evaluate information systems in organizations, such as DeLone and McLean's Model of Information Systems Success (MISS) [27]. This approach focuses on evaluating information system quality and implementation in an organizational context. This model focuses on evaluating information systems from the users' perspectives, via three main domains: 1) variables for evaluating the quality of the system, the quality of the information provided, and the quality of the service provided to users via the implementation of the system; 2) both system use and user satisfaction; and, 3) the perceived benefits to the health service in which the system was implemented.

The MISS has been used around the world in the evaluation of EMR systems and other eHealth components generating evidence about the validity of this application in different contexts [45] [46] [47] [48] [49] [50] [51] [52] [53]. The objective of the present study was to explore the use of the MISS to evaluate an EMR implemented in the public health services of Aguascalientes, as a case study that could inform its application in other health institutions of Mexico.

## MATERIALS AND METHODS

### Study design and theoretical model

The case study design [54] applied in the present study used, as a theoretical guide, DeLone and McLean's Model of Information Systems Success (MISS), particularly its most recent update [27].

### Study setting

The present study was performed at the *Instituto de Servicios de Salud del Estado de Aguascalientes (ISSEA)*, which is the main health service provider for the population in the state not covered by social security. In 2015, the total population of Aguascalientes was estimated at 1,292,901 inhabitants, of whom an estimated 42.9% do not have social security coverage [55]. The ISSEA comprises the following: 21 urban health centers (*Centros de Salud Urbanos* or CSUs); and, 62 rural health centers (*Centros de Salud Rurales* or CSRs) providing primary care across three sanitary jurisdictions. The ISSEA has six second-level hospitals (385 beds in total) and one third-level hospital (60 beds in total) [56]. A previous published study described with more detail the healthcare provision system of the ISSEA and the general e-Health ecosystem that have been implemented [57].

The EMR system has been progressively implemented in all the primary care clinics and emergency services functioning at the second and third level of care. The advances in EMR development at the ISSEA are shown

in Table 1. The EMR consists of four main modules: 1) Patient registration and payment; 2) Medical consultation; 3) Pharmacy; and, 4) Statistics. The findings presented in Table 1 reveal the significant development of the EMR system [57], with the users of these EMR modules comprising the following, respectively: 1) Administrative and management personnel; 2) Physicians; 3) Pharmacy technicians; and, 4) Administrative personnel (statisticians).

**TABLE 1. Development of the EMR in the study setting.**

Patient Registration and Payment
<ul style="list-style-type: none"> <li>• Registration of service users.</li> <li>• Identification of user affiliation to other health subsystems and special programs.</li> <li>• User identification via a unique identifier (Clave Única de Registro de Población – CURP, or Unique Population Registry Code).</li> <li>• Administration of fees for service provision</li> <li>• Schedule for medical appointments.</li> <li>• Human resources administration.</li> </ul>
Medical Consultation
<ul style="list-style-type: none"> <li>• Integrated padlocks that automatically issue patient-dependent reminders for screening and health prevention activities.</li> <li>• Integrated clinical information requests to promote proper patient management or control (mainly chronic disease patients).</li> <li>• Integrated alerts or recommendations to improve the quality of care (prompts for referrals to specialists once need has been identified based on clinical parameters).</li> <li>• Links to medical diagnostic catalogs.</li> <li>• Provision of information about patient drug coverage (based on their membership of particular programs)</li> <li>• Provision of pharmacy stock information.</li> <li>• Incorporation of clinical practice guidelines and medication information.</li> <li>• Provision of information on recommended dosages in order to make dosage adjustments and promote the reasonable use of medication.</li> </ul>
Pharmacy
<ul style="list-style-type: none"> <li>• Provision of information on the essential medication chart (<i>Cuadro Básico de Medicamentos</i>).</li> <li>• Support for the management of stocks of medication and other health supplies.</li> </ul>
Statistics
<ul style="list-style-type: none"> <li>• Provision of the necessary forms for maintaining the monthly health service provision reports and compiling epidemiological statistics.</li> </ul>

Source: Prepared by the author.

### Sampling of medical personnel

In particular, the medical consultation module of the EMR was evaluated from the perspective of medical personnel either working or providing services in ISSEA CSU or CSR primary care health centers. Physicians were selected as informants, as it is, they

who use said module of the EMR. A convenience sample was obtained based on physicians working as medical directors or in charge of personnel in each health center of the state’s sanitary jurisdictions I and III in the period August 2018 to April 2019. In circumstances where the medical director was not available as an informant, medical personnel were included as informants in the sample, in their stead. The inclusion criterion was to have worked or to be currently working with the EMR system.

### Data collection

An adaptation of the online questionnaire developed by Canada Health Infoway, which is based on the Benefits Evaluation Framework and the MISS, was applied in the present study as an instrument for evaluating the EMR [46] [58] [59]. Some items from the questionnaire were selected, translated into Spanish and placed on a Google Forms sheet, which was sent to the informants of the study. The variables included in the model were mainly measured using five-level Likert scales, only the use variable was measured through a proposed 10-level scale. A description of the variables and items included in the instrument is shown in Annex 1.

### Data analysis

The data collected was analyzed using STATA 15 software, with Structural Equations Modeling (SEM) analysis used to test the theoretical model comprehensively. Adjustments were implemented in order to optimize the model according to suggestions provided by the software. The model was tested using the maximum likelihood method and the Satorra-Bentler method for standard error computation [60].

### Ethical considerations

The research protocol was reviewed and approved by the Research Management of the *Centro de Investigación e Innovación en Tecnologías de la Información y Comunicación* (INFOTEC or Center for Research and Innovation in Information and Communication

Technologies). Prior to responding to the survey, the informants were informed about the research objectives and those responsible for the study. All informants gave their consent to participate in the study. The identity of the informants was protected using alphanumeric codes.

## RESULTS AND DISCUSSION

### Sample characteristics

The sample characteristics are shown in Table 2. A total of 62 physicians answered the online questionnaire, working at a total of 46 health centers, namely 88.5 % of all the primary care health centers, comprising a total of 52 health centers (15 CSUs and 37 CSRs) in sanitary jurisdictions I and III. Moreover, these represented 38.3 % of the 162 physicians working at these health centers, as previously reported by the SSA [56]. This sample comprised mainly qualified general medical practitioners (66.1%), although the sample also included personnel who had yet to qualify and were carrying out their one-year period of social service (30.6%). The majority had worked with the EMR system for more than three years (46.8%), meaning that, therefore, they were qualified physicians.

### Measurement of the MISS variables

The results for the measurement of the MISS variables via their respective items are shown in Table 3. As can be seen, means above three were obtained for all items on the five-level Likert scale used in the present study. The lowest means were obtained for two items related to service quality (SQ1 and SQ2, with means of 3.27 and 3.15, respectively), while the highest means were obtained for items related to system quality (SQ5, with a mean of 4.08) and net perceived benefits (NB5 and NB6, with means of 4.05 and 4.11, respectively). It should be noted that the four MISS variables that were measured using Likert items showed high internal consistency values (Coefficient > 0.85).

**TABLE 2. Descriptive statistics of the medical staff surveyed (n=62).**

Data	n (%)
<b>Sanitary Jurisdiction</b>	
I	40 (64.5)
III	22 (35.5)
<b>Age</b>	
< 20	1 (1.6)
21 to 30	22 (35.5)
31 to 40	10 (16.1)
41 to 50	18 (29.0)
51 to 60	8 (12.9)
> 61	3 (4.8)
<b>Sex</b>	
Female	24 (38.7)
Male	38 (61.3)
<b>Education</b>	
Non-qualified physician (social service)	19 (30.6)
General medical practitioner	41 (66.1)
Specialist physician	1 (1.6)
Master's degree in Public Health	1 (1.6)
<b>Health service type</b>	
Rural (CSR)	39 (62.9)
Urban (CSU)	23 (37.1)
<b>Time working with EMR</b>	
< 1 month	2 (3.23)
1 to 3 months	10 (16.1)
4 to 6 months	6 (16.1)
7 to 12 months	7 (11.3)
1 to 2 years	8 (12.9)
> 3 years	29 (46.8)
<b>Total</b>	<b>62 (100)</b>

NOTES:

Source: Prepared by the author.

### Estimations for the MISS

The structural model tested is shown in Figure 1, while the results of the calculation of direct and indirect effects are shown in Table 4. As can be seen, in terms of the dependent variable of *use*, only *system quality* was a significant variable ( $\beta = 0.389$ ). With regard to the dependent variable of *user satisfaction*, the effects of *system quality* ( $\beta = 0.907$ ) and *service quality* ( $\beta = 0.331$ ) were significant, while, in terms of the dependent variable of *net benefits*, only *user satisfaction* was significant ( $\beta = 0.728$ ). The values of the coefficient of determination ( $R^2$ ) were high for *user satisfaction* and *net benefits* (0.931 and 0.877, respectively), but low for *use* (0.413).

**TABLE 3. Measurement of the variables from the Model of Information Systems Success (MISS).**

Variable	Item <sup>a</sup>	No <sup>b</sup>		Mean	Standard Deviation	Coefficient $\alpha^c$
<b>System Quality</b>	SQ1	L5	The EMR is easy to use	3.94	0.14	0.9503
	SQ2	L5	The effort required to complete an action or access information in the EMR is acceptable	3.84	0.13	
	SQ3	L5	The EMR response time is acceptable	3.84	0.13	
	SQ4	L5	The EMR is integrated with my workflow	3.76	0.14	
	SQ5	L5	The access to the EMR is acceptable	4.08	0.12	
	SQ6	L5	The characteristics of the EMR enable me to perform my job well	3.63	0.14	
	SQ7	L5	The EMR is consistent in its performance	3.64	0.13	
	SQ8	L5	In general, the quality of the EMR is excellent	3.42	0.14	
<b>Information Quality</b>	IQ1	L5	The information provided by the EMR is complete	3.71	0.13	0.9410
	IQ2	L5	The information provided by the EMR is timely	3.95	0.11	
	IQ3	L5	The information provided by the EMR is appropriate	3.87	0.12	
	IQ4	L5	The information provided by the EMR is relevant	3.97	0.11	
	IQ5*	L5	The information provided by the EMR is available when needed	3.79	0.13	
	IQ6	L5	The information provided by the EMR enables me to make patient care decisions or recommendations more quickly	3.69	0.14	
<b>Service Quality</b>	SQ1	L5	The current level of EMR training is acceptable	3.27	0.15	0.8584
	SQ2	L5	The level of ongoing support provided for the use of the EMR is acceptable	3.13	0.15	
<b>Use</b>	U1	N10	On a scale of 0 to 10, What amount do you use the EMR for patient care?	8.7	0.27	1
<b>User Satisfaction</b>	US1	L5	Overall, how satisfied are you with the EMR?	3.8	0.13	1
<b>Net Benefits</b>	NB1	L5	The EMR improves my productivity	3.69	0.14	0.9128
	NB2	L5	The EMR improves the quality of care I provide	3.56	0.16	
	NB3	L5	The EMR makes my job easier	3.71	0.15	
	NB4	L5	The EMR improves our capacity for continuous patient care	3.74	0.14	
	NB5*	L5	The EMR improves our ability to share patient information among healthcare staff	4.05	0.12	
	NB6*	L5	The EMR improves the efficiency of requesting laboratory tests, and X-rays, as well as generating prescriptions	4.11	0.11	
	NB7	L5	The EMR improves the quality of my decision-making	3.43	0.15	
	NB8	L5	The EMR reduces fragmentation in the care provided to my patients and facilitates their mobility on the continuum of care	3.53	0.14	
	NB9	L5	The EMR reduces risks to patient safety	3.89	0.13	

NOTES:

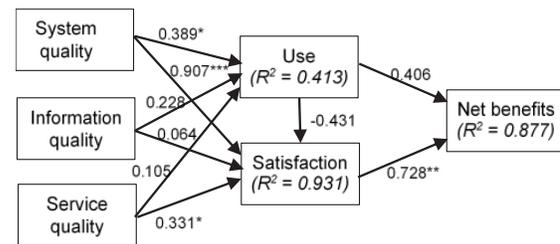
<sup>a</sup>Item eliminated in order to improve the internal consistency of the respective variable (Coefficient  $\alpha$ ) and facilitate model adjustment

<sup>b</sup>Number of categories used for the item response: L5 – Likert scale of 5 categories; and, N – numeric scale

<sup>c</sup>Coefficient  $\alpha$  obtained after model adjustment

Source: Prepared by the author.

Model adjustments were made by means of the software used in the present study, with some items (IQ5, NB5, and NB6) excluded, thus enabling better reliability and model fit. Through the adjustments made, a model was obtained that meets some of the criteria suggested in the literature [60], such as the significance of the Chi<sup>2</sup> statistical test (p < 0.000), Chi<sup>2</sup>/df < 2 (result = 1.47) and the SRMR indicator < 0.1 (result = 0.068). Also, this model was near to meet other criteria such as RMSEA < 0.05 (result = 0.110) and CFI > 0.95 (result = 0.877) indicators.



<sup>a</sup>The rectangles represent the variables comprising the MISS, while the arrows show the direct effects of independent variables on the dependent variables of this model (the indirect and total effects are described in Table 4).  
<sup>b</sup>Statistical significance of the path coefficients: \* p<0.05; \*\*p<0.01; and, \*\*\*p<0.001  
Source: Prepared by the author.

FIGURE 1. Adjusted MISS.<sup>a,b</sup>

TABLE 4. Direct, indirect and total effects on the dependent variables obtained in the adjusted model.<sup>a</sup>

A Predicts B		Standardized Effects		
A	B	Direct	Indirect	Total
System quality	Use	0.389**	----	0.389**
Information quality	Use	0.228	----	0.228
Service quality	Use	0.105	----	0.105
System quality	User satisfaction	0.907***	-0.168	0.739***
Information quality	User satisfaction	0.064	-0.098	-0.034
Service quality	User satisfaction	0.331*	-0.045	0.286**
Use	User satisfaction	-0.431	----	-0.431
System quality	Net benefits	----	0.696***	0.696***
Information quality	Net benefits	----	0.068	0.068
Service quality	Net benefits	----	0.251**	0.251**
Use	Net benefits	0.406	-0.314	0.092
User satisfaction	Net benefits	0.728*	----	0.728*

NOTES:  
<sup>a</sup>Statistical significance levels: \* p<0.05; \*\*p<0.01; and, \*\*\*p<0.001  
Source: Prepared by the author.

### Improvement opportunities for the EMR

Various improvement opportunities were identified from the physicians' perspectives, principally regarding the medical consultation module (Table 5). Some of the most significant suggestions made by the physicians were: 1) The continuous updating of informa-

tion, such as diagnostic catalogs, stock information, and information pertaining to the co-payment systems for drug catalogs; 2) The implementation of interoperable information systems between the second and third levels of care to improve the availability of information (i.e., results of laboratory tests performed in hospital and counter-referral information); 3) The automation of the monthly reporting of institutional statistics, including the data taken from private sector information systems (Fundación Carlos Slim [38] [61]).

TABLE 5. Opportunities for improving the EMR from the physicians' perspective.

Medical Consultation
<ul style="list-style-type: none"> <li>• Continuous updating of the diagnostics catalogs and improved participation of medical staff in this endeavor.</li> <li>• Continuous updating of the clinical practice guidelines.</li> <li>• Implementation of interoperable information systems between the second and third levels of care, which will improve follow-up of patient referrals and counter-referrals, thus promoting integrated care and giving access to laboratory, radiology and imaging tests.</li> <li>• Implementation of systems to identify users or patients with chronic diseases who travel continuously for work purposes (i.e., migrants), to avoid limiting their medication supply.</li> <li>• Continuous monitoring of medication stock held in the pharmacy, in order that the computerized system corresponds to physical availability.</li> <li>• Continuous monitoring to prevent errors in the lists of medication covered by special programs.</li> </ul>
Statistics
<ul style="list-style-type: none"> <li>• Automation of the process for filing monthly reports, in order that the information for the monthly service provision reports is obtained automatically from the EMR. Also, for the filing of information systems that have been provided by private entities.</li> </ul>

Source: Prepared by the author.

This study used a socio-technical and psychometric approach to evaluate an EMR system by applying the MISS, a comprehensive conceptual framework. The main contribution of the study could be found in the manner in which it applied this model in the primary care physicians and in the context of the study setting.

As an approach of reliability, the data gotten from the instrument adapted for and translated into Spanish obtained good results in terms of the internal consistency (Coefficient  $\alpha$ ) in the different constructs. Besides, an structural equations model (SEM) analysis was used to study the relationship among the different variables of the MISS allowing to identify the relationship between the variables related to EMR quality (*quality of the system/quality of the information*) and implementation (*quality of the service*) and the closely related *satisfaction/use* variables, as well as the relationship with the *perceived net benefits* reported by medical personnel. However, it was not possible to prove some relationships, mainly those with the use variable, which could be due to the fact that it was measured with a single item, when there may be different modalities and dimensions of the use of the EMR by medical personnel, including the frequency, types, objectives, and quality of use.

In terms of the statements of an international consensus regarding psychometric research reporting [62], this study contributes on generating evidence about the validity of the data gotten from the adapted instrument derived from the MISS, as an approach to evaluating EMR systems in public health services in Mexico. However, it is considered that more studies should be performed in order to improve the adapted instrument and generate robust evidence taking into account the different contexts derived from the country's fragmented health system. Also, the incorporation of the perspectives of physicians working at the second or third levels of care as well as other healthcare professionals could be of great relevance to par-

ticular healthcare systems, considering the different levels of EMR implementation in the public health system. In this regard, it should be noted that various published studies have contributed too on generating evidence in this field, using the MISS, and some modified versions, in other countries at different levels of healthcare, from different health workers' perspectives, and focusing on the evaluation of different eHealth systems, such as HIS, EMR and EHR [45] [46] [47] [48] [49] [50], and PACS [51] [52] [53].

Moreover, beyond the focus on developing and validating the MISS or an integrative instrument based on it, the building of indicators from the measurement of MISS variables could also be used as a way to guide and inform the implementation of EMR systems (or other eHealth components) in healthcare institutions. Expanding on this topic, these indicators could be tested and later used in the context of eHealth or digital health policy implementation in Mexico in different contexts. It should be noted that this has been the focus of studies conducted in other countries [63] [64], some of which have focused their analysis on identifying opportunities to improve the application of these technologies [65] [66].

The following were identified as strengths of the study: 1) The use of MISS, an integrated framework that incorporates various dimensions related to the success of information systems and goes beyond the technology adoption or acceptance models; 2) The use of a structural equation model (SEM) as an analytical methodology that enables an analysis of all the model variables and their relationships (such as their direct and indirect effects); and, 3) The identification of opportunities for improving the EMR system as well as its implementation from the perspective of medical staff, through which the authorities or management can be made aware informed (a formative evaluation approach, which focuses on improving implementation [67] [68] and has been used in other eHealth studies [48]).

As weaknesses of the present study, the following were identified: 1) The case-study design was applied to only one state health service thus limiting the external validity of the study to other state health institutions (SESA, SSA), as these have implemented their own EMR systems; 2) a complete set of responses by the physicians to the questionnaire was not obtained due to the low response rate; and, 3) The need to build a more integrated measurement of the use variable.

These weaknesses are identified as further research opportunities.

### **CONCLUSION**

The present study contributes generating evidence on the use of the MISS and the adapted instrument to evaluating EMR systems in public health services of Mexico, although some improvements should be performed in this instrument. Besides, more evidence

should be generated in this field in order to promote the continuous improvement of EMR systems, in the context of the e-Health (or Digital health) policy.

### **Conflicts of interest**

The author declares that there is no conflict of interest.

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## REFERENCES

- [1] World Health Organization. e-Health (WHA58.28). In: Fifty-eighth World Health Assembly (WHA58/2005/REC/1) [Internet]. Geneva: WHO; 2005. p. 108-10. Available from: <http://www.who.int/iris/handle/10665/20398>
- [2] World Health Organization. mHealth, use of appropriate digital technologies for public health. Report by the Director-General. In: Seventy-first World Health Assembly - Provisional agenda item 124 (A71/20) [Internet]. Geneva: WHO; 2018. p. 26. Available from: [http://apps.who.int/gb/e/e\\_wha71.html](http://apps.who.int/gb/e/e_wha71.html)
- [3] World Health Organization. Digital Health. In: Seventy-first World Health Assembly - Agenda item 124 (A71/A/CONF/1) [Internet]. Geneva: WHO; 2018. p. 21. Available from: [http://apps.who.int/gb/e/e\\_wha71.html](http://apps.who.int/gb/e/e_wha71.html)
- [4] World Health Organization. WHO guideline: recommendations on digital interventions for health system strengthening [Internet]. Geneva: WHO; 2019. Available from: <https://www.who.int/reproductivehealth/publications/digital-interventions-health-system-strengthening/en/>
- [5] Aceto G, Persico V, Pescapé A. The role of Information and Communication Technologies in healthcare: taxonomies, perspectives, and challenges. *J Netw Comput Appl* [Internet]. 2018;107:125-54. Available from: <https://doi.org/10.1016/j.jnca.2018.02.008>
- [6] Mettler T, Raptis DA. What constitutes the field of health information systems? Fostering a systematic framework and research agenda. *Health Informatics J* [Internet]. 2012;18(2):147-56. Available from: <https://doi.org/10.1177/1460458212452496>
- [7] Barrett D, Liaw S-T, De Lusignan S. Unravelling the tangled taxonomies of health informatics. *J Innov Heal Informatics* [Internet]. 2014;21(3):152-5. Available from: <https://doi.org/10.14236/jhi.v21i3.78>
- [8] Boogerd EA, Arts T, Engelen LJ, van de Belt TH. "What is eHealth": time for an update? *JMIR Res Protoc* [Internet]. 2015;4(1):e29. Available from: <http://dx.doi.org/10.2196/resprot.4065>
- [9] Shaw T, McGregor D, Brunner M, Keep M, Janssen A, Barnet S. What is eHealth (6)? Development of a Conceptual Model for eHealth: Qualitative Study with Key Informants. *J Med Internet Res* [Internet]. 2017;19(10):e324. Available from: <https://dx.doi.org/10.2196%2Fjmir.8106>
- [10] Elbert NJ, Van Os-Medendorp H, Van Renselaar W, Ekeland AG, Hakkaart-Van Roijen L, Raat H, et al. Effectiveness and cost-effectiveness of ehealth interventions in somatic diseases: A systematic review of systematic reviews and meta-analyses. *J Med Internet Res* [Internet]. 2014;16(4):e110. Available from: <https://doi.org/10.2196/jmir.2790>
- [11] Flodgren G, Rachas A, Farmer AJ, Inzitari M, Shepperd S. Interactive telemedicine: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* [Internet]. 2015;(9):CD002098. Available from: <https://doi.org/10.1002/14651858.cd002098.pub2>
- [12] Iribarren SJ, Cato K, Falzon L, Stone PW. What is the economic evidence for mHealth? A systematic review of economic evaluations of mHealth solutions. *PLoS One* [Internet]. 2017;12(2):e0170581. Available from: <https://doi.org/10.1371/journal.pone.0170581>
- [13] Totten AM, Womack DM, Eden KB, McDonagh MS, Griffin JC, Grusing S, et al. Telehealth: mapping the evidence for patient outcomes from systematic reviews [Internet]. Rockville, MD: Agency for Healthcare Research and Quality; 2016. Available from: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm)
- [14] World Health Organization. Atlas of eHealth country profiles: the use of eHealth in support of universal health coverage, based on the findings of the third global survey on eHealth 2015 [Internet]. Geneva: WHO; 2016. Available from: [http://www.who.int/goe/publications/atlas\\_2015/en/](http://www.who.int/goe/publications/atlas_2015/en/)
- [15] World Health Organization, International Telecommunication Union. National eHealth Strategy Toolkit [Internet]. Geneva: WHO; 2012. Available from: <https://apps.who.int/iris/handle/10665/75211>
- [16] Organización Panamericana de la Salud. Estrategia y plan de acción sobre eSalud (2012-2017) [Strategy and plan of action on eHealth 2012-2017] [Internet]. 2011. Available from: [http://www.paho.org/ict4health/index.php?option=com\\_content&view=article&id=54:estrategia-y-plan-de-accion-sobre-esalud-2012-2017&Itemid=&lang=es](http://www.paho.org/ict4health/index.php?option=com_content&view=article&id=54:estrategia-y-plan-de-accion-sobre-esalud-2012-2017&Itemid=&lang=es)
- [17] Organización Panamericana de la Salud. La eSalud en la región de las américas : derribando las barreras a la implementación. Resultados de la Tercera Encuesta Global de eSalud de la Organización Mundial de la Salud [eHealth in the Americas region: breaking down the barriers to implementation. Results of the Third Global Survey on eHealth of the World Health Organization] [Internet]. Washington, D.C.: OPS; 2016. Available from: <http://iris.paho.org/xmlui/handle/123456789/31287>
- [18] Organization for Economic Cooperation and Development (OECD). Improving Health Sector efficiency: The Role of Information and Communication Technologies. Paris: OECD; 2010. Available from: <https://doi.org/10.1787/2074319x>
- [19] Comisión Económica para América Latina y el Caribe (CEPAL). Salud electrónica en América Latina y el Caribe: avances y desafíos [Electronic health in Latin America and the Caribbean: progress and challenges] [Internet]. Fernández A, Oviedo E, editors. Santiago de Chile: Comisión Económica para América Latina y el Caribe (CEPAL), Naciones Unidas; 2010. Available from: <https://www.cepal.org/es/publicaciones/salud-electronica-en-america-latina-y-el-caribe-avances-y-desafios>
- [20] Palacios J, Flores-Roux E, García Zaballos A. Diagnóstico del sector TIC en México, Conectividad e inclusión social para la mejora de la productividad y el crecimiento económico [Diagnosis of the ICT sector in Mexico, Connectivity and social inclusion for the improvement of productivity and economic growth] [Internet]. Documento de debate IDB-DP-235. Banco Interamericano de Desarrollo (IDB); 2013. Available from: <https://publications.iadb.org/es/diagnostico-del-sector-tic-en-mexico-conectividad-e-inclusion-social-para-la-mejora-de-la>
- [21] World Health Organization. Classification of Digital Health Interventions v 1.0, a shared language to describe the uses of digital technology for health [Internet]. Geneva: WHO; 2018. Available from: <http://www.who.int/iris/handle/10665/260480>
- [22] Díaz de León-Castañeda C. Electronic health (e-Health): a conceptual framework for its implementation in health services facilities. *Gac Med Mex* [Internet]. 2019;155(2):161-8. Available from: <https://doi.org/10.24875/GMM.M19000251>

- [23] Glasgow RE, Phillips SM, Sanchez MA. Implementation science approaches for integrating eHealth research into practice and policy. *Int J Med Inform* [Internet]. 2014 Jul;83(7):e1-11. Available from: <http://dx.doi.org/10.1016/j.ijmedinf.2013.07.002>
- [24] Bergmo T. How to measure costs and benefits of eHealth interventions: An overview of methods and frameworks. *J Med Internet Res* [Internet]. 2015;17(11):e254. Available from: <http://dx.doi.org/10.2196/jmir.4521>
- [25] McNamee P, Murray E, Kelly MP, Bojke L, Chilcott J, Fischer A, et al. Designing and Undertaking a Health Economics Study of Digital Health Interventions. *Am J Prev Med* [Internet]. 2016;51(5):852-60. Available from: <http://dx.doi.org/10.1016/j.amepre.2016.05.007>
- [26] Yusof MM, Papazafeiropoulou A, Paul RJ, Stergioulas LK. Investigating evaluation frameworks for health information systems. *Int J Med Inform* [Internet]. 2008;77(6):377-85. Available from: <https://doi.org/10.1016/j.ijmedinf.2007.08.004>
- [27] Delone W, Mclean E. The DeLone and McLean Model of Information Systems Success: A Ten-Year Update. *J Manag Inf Syst* [Internet]. 2003;19(4):9-30. Available from: <https://doi.org/10.1080/07421222.2003.11045748>
- [28] Gómez-Dantés O, Sesma S, Becerril VM, Knau FM, Arreola H FJ. Sistema de Salud de México [Mexico Health System]. *Salud Publica Mex* [Internet]. 2011;53(supl 2):S220-32. Available from: <http://saludpublica.mx/index.php/spm/article/view/5043/10023>
- [29] Instituto Nacional de Estadística y Geografía (INEGI). Encuesta Intercensal 2015 [Intercensal Survey 2015] [Internet]. 2015. Available from: <http://www.beta.inegi.org.mx/proyectos/enchogares/especiales/intercensal/>
- [30] Diario Oficial de la Federación. DECRETO por el que se reforman, adicionan y derogan diversas disposiciones de la Ley General de Salud y de la Ley de los Institutos Nacionales de Salud [DECREE by which various directions of the General Health Law and the Law of the National Institutes of Health are reformed, added and repealed] [Internet]. 2019 Nov 29; Available from: [http://www.dof.gob.mx/nota\\_detalle.php?codigo=5580430&fecha=29/11/2019](http://www.dof.gob.mx/nota_detalle.php?codigo=5580430&fecha=29/11/2019)
- [31] Gobierno Federal. Estrategia Digital Nacional [National Digital Strategy] [Internet]. 2013. Available from: [https://www.gob.mx/cms/uploads/attachment/file/17083/Estrategia\\_Digital\\_Nacional.pdf](https://www.gob.mx/cms/uploads/attachment/file/17083/Estrategia_Digital_Nacional.pdf)
- [32] Mariscal Avilés J, Gil-García JR, Ramírez-Hernández F. E-Salud en México: antecedentes, objetivos, logros y retos [E-Health in Mexico: background, objectives, achievements and challenges]. *Espac Públicos* [Internet]. 2012;15(34):65-94. Available from: <http://www.redalyc.org/articulo.oa?id=67623463015>
- [33] Gertrudiz N. e-Health: the case of Mexico [e-Health: the case of Mexico]. *Lat Am J Telehealth* [Internet]. 2010;2(2):127-67. Available from: <http://cetec.medicina.ufmg.br/revista/index.php/rlat/article/view/71>
- [34] Organización Panamericana de la Salud. Conversaciones sobre eSalud. Gestión de información, diálogos e intercambio de conocimientos para acercarnos al acceso universal a la salud [Conversations about eHealth. Information management, dialogues and knowledge exchange to get closer to universal access to health] [Internet]. Washington, DC: OPS; 2014. Available from: <http://iris.paho.org/xmlui/handle/123456789/28391>
- [35] González-Rétiz ML, Pacheco-López A. Desarrollo de la telesalud en México [Development of telehealth in Mexico] [Internet]. Santiago de Chile: Comisión Económica para América Latina y el Caribe (CEPAL), Naciones Unidas; 2013. Available from: <http://hdl.handle.net/11362/4055>
- [36] Vélez-Andrade C, Rodríguez-Hernández J. Salud Móvil: Nuevos Horizontes para la Promoción de la Salud. Proyecto m-Salud para la prevención, diagnóstico oportuno y control del sobrepeso/obesidad y diabetes tipo 2 [Mobile Health: New Horizons for Health Promotion. m-Health Project for the prevention, timely diagnosis and control of overweight / obesity and type 2 diabetes]. México City: Fundación Mexicana para la Salud (Funsalud); 2018. Available from: [https://funsalud.org.mx/wp-content/uploads/2019/11/Salud-Movil\\_-Nuevos-Horizontes-para-la-Promocion-de-la-Salud.pdf](https://funsalud.org.mx/wp-content/uploads/2019/11/Salud-Movil_-Nuevos-Horizontes-para-la-Promocion-de-la-Salud.pdf)
- [37] Cabrera NI, Castro P, Demeneghi VP, Fernández L, Morales J, Sainz L, et al. mSalUV: un nuevo sistema de mensajería móvil para el control de la diabetes en México [mSalUV: a new mobile messaging system for diabetes control in Mexico]. *Rev Panam Salud Publica* [Internet]. 2014;35(5-6):371-7. Available from: <https://www.scielosp.org/pdf/rpsp/2014.v35n5-6/371-377>
- [38] Tapia-Conyer R, Gallardo-Rincón H, Saucedo-Martínez R. CASALUD: An innovative health-care system to control and prevent non-communicable diseases in Mexico. *Perspect Public Health* [Internet]. 2015;135(4):180-90. Available from: <https://doi.org/10.1177/1757913913511423>
- [39] Tapia-Conyer R, Saucedo-Martínez R, Mujica-Rosales R, Gallardo-Rincón H, Campos-Rivera PA, Lee E, et al. Enablers and inhibitors of the implementation of the Casalud Model, a Mexican innovative healthcare model for non-communicable disease prevention and control. *Heal Res Policy Syst* [Internet]. 2016;14(1):1-12. Available from: <http://dx.doi.org/10.1186/s12961-016-0125-0>
- [40] Gallardo-Rincón H, Saucedo-Martínez R, Mujica-Rosales R, Lee EM, Israel A, Torres-Beltrán B, et al. Online continuing medical education as a key link for successful noncommunicable disease self-management: The CASALUDTM Model. *Diabetes, Metab Syndr Obes Targets Ther* [Internet]. 2017;10:443-55. Available from: <https://doi.org/10.2147/DMSO.S137891>
- [41] Hernández-Ávila JE, Palacio-Mejía LS, Lara-Esqueda A, Silvestre E, Agudelo-Botero M, Diana ML, et al. Assessing the process of designing and implementing electronic health records in a statewide public health system: The case of Colima, Mexico. *J Am Med Informatics Assoc* [Internet]. 2013;20(2):238-44. Available from: <http://dx.doi.org/10.1136/amiajnl-2012-000907>
- [42] González-Block M, Lopez-Santibañez C, Aguilera Aburto N, Aldama A, Barajas M, Becerril Montekio V, et al. Evaluación y estrategias de portabilidad y convergencia hacia la integración del Sistema Nacional de Salud, resumen ejecutivo [Evaluation and strategies of portability and convergence towards the integration of the National Health System, Executive summary] [Internet]. Cuernavaca: Instituto Nacional de Salud Pública; 2011. Available from: [http://pliopencms05.salud.gob.mx:8080/BasesCDI/Archivos/Informes/portabilidad\\_convergencia.pdf](http://pliopencms05.salud.gob.mx:8080/BasesCDI/Archivos/Informes/portabilidad_convergencia.pdf)
- [43] Fernández Morales K, McAnally Salas L, Vallejo Casarín A. Apropiación tecnológica: una visión desde los modelos y las teorías que la explican [Technological appropriation: a view from the models and theories that explain it]. *Perspect Educ* [Internet]. 2015;54(2):109-25. Available from: <https://doi.org/10.4151/07189729-Vol.54-Iss.2-Art.331>
- [44] Korpelainen K. Theories of ICT system implementation and adoption - a critical review [Internet]. Helsinki: School of Science and Technology, Aalto University; 2011. Available from: <https://aaltodoc.aalto.fi/handle/123456789/5019>

- [45] Yu P, Qian S. Developing a theoretical model and questionnaire survey instrument to measure the success of electronic health records in residential aged care. *PLoS One* [Internet]. 2018;13(1):e0190749. Available from: <https://doi.org/10.1371/journal.pone.0190749>
- [46] Tharmalingam S, Hagens S, Zelmer J. The value of connected health information: perceptions of electronic health record users in Canada. *BMC Med Inform Decis Mak* [Internet]. 2016;16(1):93. Available from: <http://dx.doi.org/10.1186/s12911-016-0330-3>
- [47] Raymond L, Paré G, Ortiz de Guinea A, Poba-Nzaou P, Trudel M-C, Marsan J, et al. Improving performance in medical practices through the extended use of electronic medical record systems: a survey of Canadian family physicians. *BMC Med Inform Decis Mak* [Internet]. 2015;15(1):27. Available from: <https://doi.org/10.1186/s12911-015-0152-8>
- [48] Bossen C, Jensen LG, Udsen FW. Evaluation of a comprehensive EHR based on the DeLone and McLean model for IS success: Approach, results, and success factors. *Int J Med Inform* [Internet]. 2013;82(10):940-53. Available from: <https://doi.org/10.1016/j.ijmedinf.2013.05.010>
- [49] Messeri P, Khan S, Millery M, Campbell A, Merrill J, Shih S, et al. An Information Systems Model of the Determinants of Electronic Health Record Use. *Appl Clin Inform* [Internet]. 2013;4(2):185-200. Available from: <http://dx.doi.org/10.4338/ACI-2013-01-RA-0005>
- [50] Alharthi H, Youssef A, Radwan S, Al-Muallim S, Zainab A-T. Physician satisfaction with electronic medical records in a major Saudi Government hospital. *J Taibah Univ Med Sci* [Internet]. 2014;9(3):213-8. Available from: <https://doi.org/10.1016/j.jtumed.2014.01.004>
- [51] Tzeng WS, Kuo KM, Lin HW, Chen TY. A Socio-technical assessment of the success of picture archiving and communication systems: The radiology technologist's perspective. *BMC Med Inform Decis Mak* [Internet]. 2013;13(1):1. Available from: <http://dx.doi.org/10.1186/1472-6947-13-109>
- [52] Sicotte C, Paré G, Bini KK, Moreault M-P, Laverdure G. Virtual Organization of Hospital Medical Imaging: A User Satisfaction Survey. *J Digit Imaging* [Internet]. 2010;23(6):689-700. Available from: <https://doi.org/10.1007/s10278-009-9220-x>
- [53] Paré G, Lepanto L, Aubry D, Sicotte C. Toward a multidimensional assessment of picture archiving and communication system success. *Int J Technol Assess Health Care* [Internet]. 2005;21(4):471-9. Available from: <https://doi.org/10.1017/s0266462305050658>
- [54] Yin RK. *Case Study Research: Design and Methods*. 5th ed. Thousand Oaks: SAGE Publications; 2014. 282 p.
- [55] Consejo Nacional de Evaluación de la Política de Desarrollo Social (CONEVAL). Información de Pobreza y Evaluación de las Entidades Federativas [Poverty Information and Evaluation of the Federal Entities] [Internet]. 2019. Available from: <https://www.coneval.org.mx/coordinacion/entidades/Paginas/inicioent.aspx>
- [56] Secretaría de Salud. Portal de datos abiertos de Secretaría de Salud [Open data portal of the Ministry of Health] [Internet]. 2018. Available from: <https://datos.gob.mx/busca/organization/salud>
- [57] Díaz de León Castañeda C, Góngora Ortega J. eSalud en servicios de salud públicos en México: estudio de caso [E-Health in Public Health Services in Mexico: Case Study]. *Región y Soc* [Internet]. 2020;32:e1256. Available from: <https://doi.org/10.22198/rys2020/32/1256>
- [58] Canada Health Infoway. System and use assessment survey (refresh february 2015) [Internet]. 2015. Available from: <https://www.infoway-inforoute.ca/en/component/edocman/resources/toolkits/change-management/national-framework/monitoring-and-evaluation/resources-and-tools/991-benefits-evaluation-survey-process-system-use-assessment-survey?Itemid=101>
- [59] Lau F, Hagens S, Muttitt S. A proposed benefits evaluation framework for health information systems in Canada. *Healthc Q* [Internet]. 2007;10(1):113-8. Available from: <https://www.longwoods.com/content/18657>
- [60] Stata 25 Software. *Structural Equations Modelling Reference Manual* [Internet]. 2019. Available from: <https://www.stata.com/bookstore/structural-equation-modeling-reference-manual/>
- [61] Fundación Carlos Slim. Programas de Innovación [Innovation programs] [Internet]. 2018. Available from: <https://www.salud.carlosslim.org/innovacion/>
- [62] American Educational Research Association (AERA), American Psychological Association (APA), National Council on Measurement in Education (NCME). *Standards for Educational and Psychological Testing*. Washington, DC: AERA, APA, NCME; 2014. 230 p.
- [63] Buabbas AJ, Al-Shamali DA, Sharma P, Haidar S, Al-Shawaf H. Users' Perspectives on a Picture Archiving and Communication System (PACS): An In-Depth Study in a Teaching Hospital in Kuwait. *JMIR Med Informatics* [Internet]. 2016;4(2):e21. Available from: <https://doi.org/10.2196/medinform.5703>
- [64] Otieno GO, Hinako T, Motohiro A, Daisuke K, Keiko N. Measuring effectiveness of electronic medical records systems: Towards building a composite index for benchmarking hospitals. *Int J Med Inform* [Internet]. 2008;77(10):657-69. Available from: <https://doi.org/10.1016/j.ijmedinf.2008.01.002>
- [65] Kuo K, Liu C, Talley PC, Pan S. Strategic Improvement for Quality and Satisfaction of Hospital Information Systems. *J Healthc Eng* [Internet]. 2018:1-14. Available from: <https://doi.org/10.1155/2018/3689618>
- [66] Cohen JF, Coleman E, Kangethe MJ. An importance-performance analysis of hospital information system attributes: A nurses' perspective. *Int J Med Inform* [Internet]. 2016;86:82-90. Available from: <http://dx.doi.org/10.1016/j.ijmedinf.2015.10.010>
- [67] Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. *BMC Psychol* [Internet]. 2015;3(1):32. Available from: <https://doi.org/10.1186/s40359-015-0089-9>
- [68] Lau F, Kuziemsy C, Price M, Gardner J. A review on systematic reviews of health information system studies. *J Am Med Informatics Assoc* [Internet]. 2010;17(5):637-45. Available from: <https://doi.org/10.1136/jamia.2010.004838>

## ANNEXES

### ANNEX 1. Instrument for the Variables Measurement of the Model of Information Systems Success (MISS).

Variable/Items	Strongly disagree	Moderately disagree	Neither agree nor disagree	Moderately agree	Strongly agree
<b>System quality<sup>a</sup></b>					
The EMR is easy to use	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The effort required to complete an action or access information in the EMR is acceptable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR response time is acceptable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR is integrated with my workflow	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The access to the EMR is acceptable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The characteristics of the EMR enable me to perform my job well	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR is consistent in its performance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
In general, the quality of the EMR is excellent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Information quality<sup>a</sup></b>					
The information provided by the EMR is complete	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information provided by the EMR is timely	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information provided by the EMR is appropriate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information provided by the EMR is relevant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information provided by the EMR is available when needed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information provided by the EMR enables me to make patient care decisions or recommendations more quickly	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Service quality<sup>a</sup></b>					
The current level of EMR training is acceptable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The level of ongoing support provided for the use of the EMR is acceptable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>User satisfaction<sup>a</sup></b>					
Overall, how satisfied are you with the EMR?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Perceived net benefits<sup>a</sup></b>					
The EMR improves my productivity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR improves the quality of care I provide	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR makes my job easier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR improves our capacity for continuous patient care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR improves our ability to share patient information among healthcare staff	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR improves the efficiency of requesting laboratory tests, and X-rays, as well as generating prescriptions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR improves the quality of my decision-making	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR reduces fragmentation in the care provided to my patients and facilitates their mobility on the continuum of care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The EMR reduces risks to patient safety	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Use<sup>b</sup></b>					
On a scale of 0 to 10, What amount do you use the EMR for patient care?					
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6
7	8	9	10		

NOTES:

<sup>a</sup> Variables measured through five-level Likert scales. Items taken or adapted from Canada Health Infoway survey [].

<sup>b</sup> This variable was measured from a 10 point scale, proposed in this study.

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## Análisis Biomecánico de una Prótesis de Cadera mediante Elementos Finitos

### Biomechanical Analysis of a Hip Prosthesis Using a Finite Elements

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#### RESUMEN

En el presente trabajo se plantea un análisis biomecánico de una prótesis de cadera bajo condiciones de cargas estáticas asociadas a actividades cotidianas, en el cual se comparan tres materiales metálicos para la fabricación de una prótesis personalizada a partir de imágenes médicas. Se utilizaron plataformas en la nube de diseño asistido por computadora y de análisis por elementos finitos. Se diseñaron dos modelos de la prótesis a analizar, uno hueco y otro sólido mediante curvas spline paramétricas. Para el análisis biomecánico se requirió un tamaño de malla de 2,537,684 de elementos tetraédricos y 471,335 nodos para estudiar ocho casos de posturas para una persona de 75 kg de peso, mismos que se analizaron tomando como materiales base acero inoxidable 316L, aleación Ti-6Al-4V y L-605. Se observó que con actividades tales como trotar, subir y bajar escaleras los materiales 316L y L-605, presentan el riesgo de deformación plástica e inclusive fractura. Los resultados mostraron que el material más idóneo para la fabricación de este tipo de prótesis es el Ti-6Al-4V, además de que este nos permite realizar modelos tanto sólidos como huecos, suponiendo este último, un ahorro de material y proporcionando mayor ligereza en la prótesis.

**PALABRAS CLAVE:** Análisis biomecánico; Diseño asistido por computadora; Elementos finitos; Prótesis de cadera

### ABSTRACT

This paper shows a biomechanical analysis of a hip prosthesis under conditions of static loads associated with daily activities. For which it compared three metallic materials for the manufacture of a customized prosthesis from medical images, it was used cloud platforms with computer-aided design and finite element analysis. Two models of prosthesis one hollow and the other one solid using parametric spline curves were designed and analyzed. The biomechanical analysis required a mesh size consisting of 2,537,684 tetrahedral elements and 471,335 nodes to study eight cases of postures for a person weighing 75 kg. These cases were analyzed based on 316L stainless steel, Ti-6Al-4V alloy, and another L-605 alloy. It was observed that with activities such as jogging, climbing and descending stairs, materials 316L, and L-605 present the risk of plastic deformation and even fracture. The results show that the most suitable material for the manufacture of this type of prosthesis is the Ti-6Al-4V, which allows us to make both solid and hollow models. Assuming this last material is saved and improves the prosthesis lightness.

**KEYWORDS:** Biomechanical analysis; Computer-aided design; Finite elements; Hip prosthesis

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## INTRODUCCIÓN

El tema de prótesis de cadera actualmente es un tópico de estudio a nivel mundial, primeramente, porque las lesiones de cadera son un padecimiento muy recurrente, y, en segundo lugar, debido a que estas cirugías son las que han tenido mayor éxito en el reemplazo total o parcial. Además, la creciente población de adultos mayores, las inherentes fracturas asociadas a la edad y la osteoporosis, hacen centrar nuestra atención en atender las necesidades en cuanto a la reparación de las fracturas, mediante el análisis biomecánico y el diseño asistido por computadora.

Las prótesis de cadera han ido evolucionando a través del tiempo, desde la primera implementación de las prótesis de cadera en el año de 1960, han variado en las formas y en los materiales, desde aceros de grado quirúrgico hasta aleaciones de cromo, cobalto, níquel y titanio, entre otros; todas con la intención de proponer un modelo eficaz para la aceptación completa del cuerpo humano de un miembro no perteneciente a él <sup>[1]</sup>.

Actualmente, el concepto básico de Charnley de artroplastia de baja fricción y la utilización del par metal-polietileno es el estándar de la artroplastia total de cadera. Los resultados clínicos de la prótesis de Charnley son hoy día referencia obligada para evaluar el rendimiento de otras artroplastias <sup>[1]</sup>.

Las prótesis actuales, presentan un tratamiento superficial, el cual da un aspecto rugoso, en una pequeña sección el vástago y en el componente acetabular, cubierto con hidroxapatita. Lo anterior con el propósito de favorecer la osteointegración, es decir la integración del tejido óseo a la prótesis, ya que los osteoblastos reconocen a la hidroxapatita como si fuera hueso puesto que es el componente mineral de éste.

A diferencia de otras prótesis, las prótesis de cadera deben soportar los esfuerzos en actividades normales, caminar o subir escaleras, las cuales pueden superar

cuatro veces el peso corporal del individuo implantado y en algunos casos 10 veces, por ejemplo, ante un tropezón. Todo supone un compromiso entre ligereza, diseño y las propiedades mecánicas de los materiales con que se fabrican las prótesis.

La exigencia de dichas solicitaciones nos obliga a buscar nuevos diseños y materiales. Tal es el caso de la aleación Ti-6Al-4V ampliamente utilizada para la fabricación de prótesis osteoarticulares. Las prótesis de Ti-6Al-4V presentan como principales ventajas: baja densidad, buenas propiedades mecánicas, gran biocompatibilidad, elevada resistencia a la corrosión y a la fatiga.

Otros materiales cuya aplicación es muy amplia, como en las placas temporales de osteosíntesis, tornillos, clavos y fijadores, además de prótesis de cadera son los aceros con contenidos de carbono de 0.08% como el AISI 316 o inferiores al 0.03% como el AISI 316L. Este material tiene como ventaja el ser de más bajo costo que las aleaciones de Titanio.

Así mismo, la aleación L605 que está formada por cobalto, cromo, wolframio y níquel. Esta aleación presenta una alta resistencia a la corrosión y en los últimos años sus usos se han ampliado al campo de las endoprótesis vasculares, así como en la elaboración de stent y prótesis de cadera. Razón por la cual se ha considerado en el presente estudio.

Si bien es cierto, el avance científico en cuanto al desarrollo de materiales metálicos biocompatibles o bioinertes ha sido gradual, existe una gran diferencia con la biomecánica computacional que ha avanzado aceleradamente, desde su implementación hasta hoy en día. Lo anterior nos ha permitido reemplazar los ensayos en gran escala por simulaciones numéricas para reducir costos económicos, así como ensayos en animales. Al incorporarse la biomecánica computacional a la industria 4.0, que estamos viviendo actual-

mente, nos permite encontrar mejores soluciones a la investigación de una manera más eficiente, con mayores beneficios que la investigación convencional. Todo ello al reducir el tiempo de análisis, la optimización del equipo de cómputo disponible y derribar barreras espaciales con los entornos colaborativos.

Algunos autores se han centrado en realizar análisis de prótesis de cadera bajo determinadas condiciones de carga, con el propósito de poder determinar la resistencia a la fatiga de dichas prótesis [2] [3]. También se han realizado ensayos con fluidos corporales simulados para estudiar el efecto de la corrosión y la fatiga de manera conjunta [4] [5]. Al mismo tiempo, se ha investigado también el efecto que el apantallamiento de tensiones tiene sobre la interface prótesis-hueso [6] [7] [8]. Con respecto al estudio de prótesis mediante elementos finitos, podemos decir que las investigaciones van desde estudios comparativos de prótesis comerciales [9], hasta diseños completamente nuevos e innovadores [8] [10] [11] [12]. Sin embargo, la investigación en torno al análisis por elementos finitos en la nube es escaso.

El objetivo de este trabajo, es determinar el desempeño biomecánico de una prótesis de cadera bajo condiciones de cargas asociadas a actividades cotidianas. En el cual, se comparan tres materiales metálicos para la fabricación de una prótesis personalizada a partir de imágenes médicas, y la utilización de plataformas de diseño asistido por computadora en la nube, Onshape (Onshape Inc, Cambridge, MA); y de análisis por elementos finitos en la nube, SimScale (SimScale GmbH, München, Germany).

## METODOLOGÍA

El diseño de la prótesis personalizada requirió de información recabada previamente de imágenes médicas de un paciente anónimo con un peso de 75 kg, el cual estaba hospitalizado en el Instituto Mexicano del Seguro Social y que donó sus imágenes médicas para realizar la presente investigación mediante una carta

de consentimiento informado. Se obtuvo un modelo tridimensional del hueso fémur con dichas imágenes y mediante segmentación de cada corte tomográfico en 3DSlicer (3Dslicer.org, Boston, MA). Derivado de dicha segmentación, se conocieron las medidas del perfil del hueso que permitieron crear las geometrías del modelo de prótesis. Las geometrías se desarrollaron con curvas SPLINE a través de la plataforma de diseño en la nube llamada Onshape. En la Figura 1 se muestra el modelo de prótesis creado, así como sus componentes principales indicados con distintos colores. La Figura 1 muestra además un modelo isométrico del vástago. Y finalmente en la Figura 2 se muestran las dimensiones obtenidas de las imágenes médicas que permitieron crear la geometría de la prótesis.

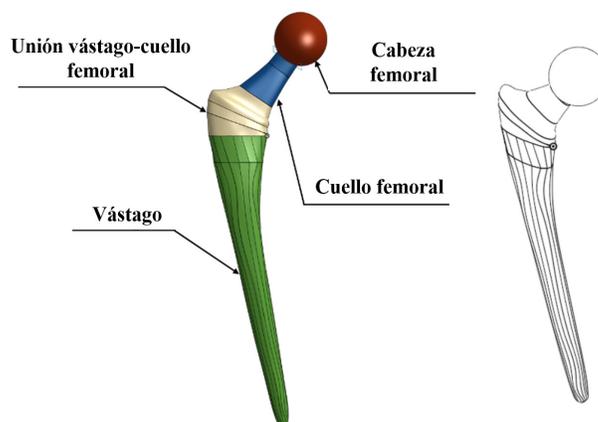


FIGURA 1. Partes de la prótesis y modelo isométrico.

Debido a la complejidad de la forma de la prótesis se requirieron diferentes geometrías de acuerdo a cada elemento que la conforman. Para realizarla se crearon perfiles en el plano superior “TOP” a distintas distancias y a través de la función barrido “LOFT” se unieron los perfiles para crear la forma. Además, se requirieron planos inclinados adicionales de referencia para poder obtener la geometría.

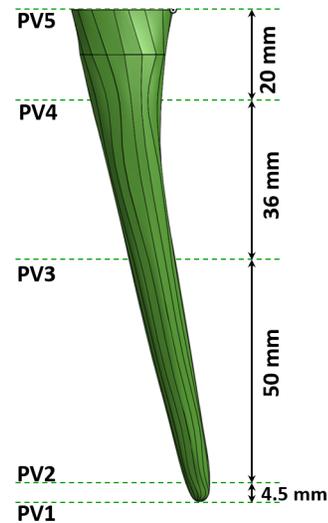
## Modelado del vástago

El vástago es el elemento que va injertado en el hueso fémur por medio de interferencia y es el único elemento con variación en los dos modelos de prótesis.

**TABLA 1. Perfiles del vástago (PV).**

PERFIL	GEOMETRÍA
PV1	
PV2	
PV3	
PV4	
PV5	

total de 110.5mm. Las distancias entre cada perfil, partiendo de la parte inferior hacia la superior, desde PV1 hasta PV5 son: 4.5 mm, 50 mm, 36 mm y 20 mm respectivamente. En el modelo hueco, la altura total de la cavidad es de 106 mm, haciendo uso de los perfiles internos con excepción del PV1.

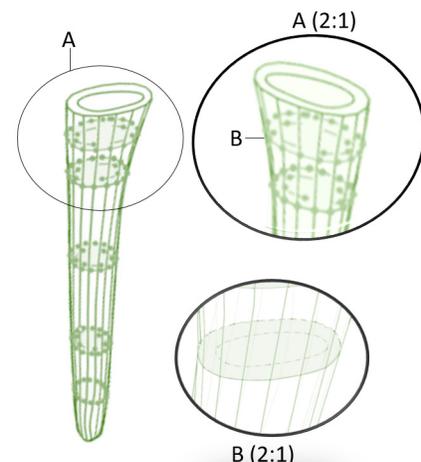


**FIGURA 2. Distancia entre perfiles del vástago.**

En la Figura 3 se muestra el modelo de prótesis hueco exhibiendo la forma de la cavidad (A) y las geometrías tanto externas como internas (B) de cada perfil.

Para el modelo sólido se requieren los 5 perfiles del vástago (PV) externos enumerados del 1 al 5 (PV1 al PV5) unidos en una sola parte totalmente sólida. En el modelo hueco, se utilizan los mismos perfiles, pero a diferencia del anterior, los perfiles internos indicados del PV2 al PV4 muestran el área y la trayectoria de la cual se extrae el material que aligera el modelo (Tabla 1). Se muestran las formas de los perfiles obtenidos de los cuales las geometrías internas son únicamente para el modelo hueco en la Tabla 1. Cada punto de la geometría de cada perfil tiene coordenadas específicas en x, y, z.

Las distancias de separación de cada perfil constituyente del vástago se muestran en la Figura 2. Tanto el modelo sólido como el modelo hueco tienen una altura



**FIGURA 3. Prótesis hueca con los perfiles y las geometrías visibles.**

### Unión vástago-cuello femoral

La unión vástago-cuello femoral tiene una altura total de 20 mm, está compuesta por 3 perfiles del cuello femoral (PCF) unidos desde su perfil inferior PCF1 con el perfil superior del vástago PV5 (Figura 4).

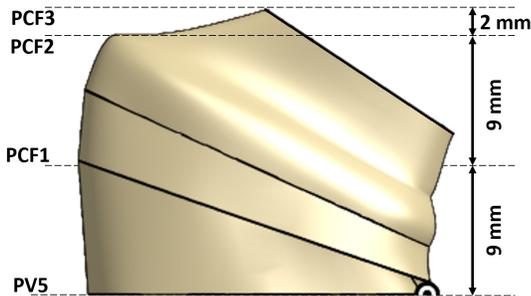


FIGURA 4. Distancia entre perfiles de unión vástago- cuello femoral.

TABLA 2. Perfiles del cuello femoral.

PERFIL	GEOMETRÍA
PCF1	
PCF2	
PCF3	
PCF4	

Los perfiles obtenidos para la unión del vástago con el cuello femoral se muestran en la Tabla 2 y corresponden a PCF1 al PCF3.

### Cuello femoral

Esta parte del cuello femoral es de suma importancia, ya que en esta se presentan la mayor concentración de esfuerzos. Está constituida por dos perfiles sobre planos inclinados auxiliares separados por una distancia de 20 mm, uno corresponde al perfil superior PFC3 del cuello femoral que une el perfil de este cuello de nombre PCF4 (Tabla 2). La forma obtenida es la presentada en la Figura 5.

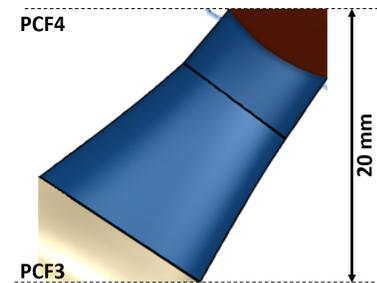


FIGURA 5. Distancia entre perfiles PCF3-PCF4.

### Cabeza femoral o cotilo

La cabeza femoral es simplemente una esfera de 23 mm de diámetro, creada encima del perfil PCF4. Se crea un plano inclinado con una línea guía de referencia en el plano x para indicar el diámetro que tendrá, y en el plano z para indicar la superficie de revolución.

### Análisis biomecánico

El análisis biomecánico de la prótesis creada fue realizado en SimScale, una plataforma de análisis en la nube vinculada con Onshape.

Para realizar el estudio biomecánico se consideraron los siguientes tópicos:

- a. *Geometría:* Modelo sólido en una sola parte realizado en Onshape.

- b. *Malla:* La malla seleccionada a través de un análisis de sensibilidad de todos los tamaños de malla que ofrece SimScale.
- c. *Material:* De los materiales seleccionados para este estudio, los datos de interés son las características mecánicas de cada uno (densidad, módulo de Young, módulo de Poisson y para posteriores comparaciones el último esfuerzo a la tensión y límite elástico).
- d. *Cargas:* La carga principal es el peso de la persona en forma de fuerza que actúa sobre la articulación de la cadera, misma que es descompuesta en sus componentes x, y, z bajo la influencia de la realización de una actividad.
- e. *Restricciones:* Se fijó el vástago en su parte inferior y en la parte superior de la cabeza femoral se aplicó la carga (Figura 6).



**FIGURA 6.** Zona de aplicación de las restricciones aplicadas al vástago mostrada en color azul.

Las actividades para analizar el comportamiento del modelo de prótesis, simulando actividades cotidianas son: caminar, de pie, andar en bicicleta, levantarse, subir escaleras, bajar escaleras, sentarse y, trotar <sup>[13]</sup>.

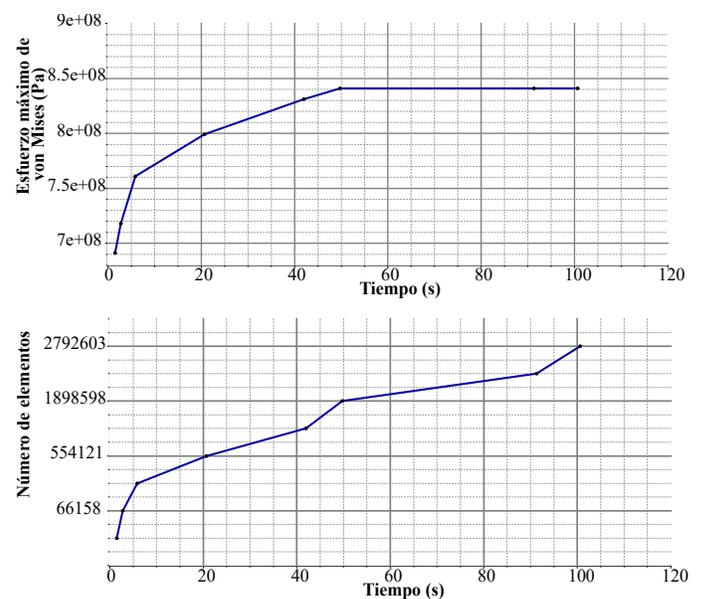
Se realizaron 56 simulaciones en SimScale, con un tiempo de cómputo de 39 minutos cada una; donde 8 de ellas sólo se realizaron para la selección de mallado óptimo, las restantes corresponden a 8 condiciones de prueba para el modelo de prótesis sólido y 8 condiciones de prueba para el modelo de prótesis hueco, y estas a su vez realizadas con 3 materiales distintos.

## Selección de mallado

Las simulaciones se realizaron con la forma tetraédrico dominante, con los tamaños de malla que van desde 32,134 hasta 2,792,603 de elementos con el modelo de prótesis sólido, para poder seleccionar la que aporta mayor precisión sin implicar un costo computacional alto.

Se realizó un análisis de sensibilidad que consistió en evaluar la densidad del mallado, es decir el número de elementos que conforman cada una de las mallas. Posteriormente se contrastaron los resultados del esfuerzo máximo de von Mises para seleccionar la densidad que ofrece una variación en los resultados inferior al 0.01 de error y brinde el menor tiempo de cómputo.

En la Figura 7 se encuentran graficados el número de elementos tetraédricos en el eje horizontal, contra los valores del esfuerzo máximo de von Mises expresado en pascles en el eje vertical. De los ocho tamaños de malla graficados se optó por la malla con 2,537,684 de elementos tetraédricos, 471,335 nodos y con un valor de von Mises de 8.416e8 Pa.



**FIGURA 7.** Gráfico de análisis de sensibilidad del mallado. Esfuerzo de von Mises y número de elementos contra tiempo.

La selección se realizó en virtud de que esta presenta poca variación con la tendencia global, además de que no representa mucho costo de tiempo de cómputo (39 min), incluyendo el tiempo de mallado, ni mucho menos consumo de memoria (7968.04 Mo) en el servidor.

### Materiales seleccionados para el análisis biomecánico

Los materiales seleccionados pertenecen a la familia de los biomateriales con aplicación específica para prótesis de cadera, debido a sus propiedades fisicoquímicas y mecánicas que son Ti-6Al-4V, 316-L y el L-605.

Se tomó como referencia los valores de las propiedades mecánicas con los cuales autores como A. Maiques Oltra [14], R. E. Arellano Guerrero [15], K. B. Hazlehurst [16], O. Martel [9], P. Losa Zapico [17], Changning Sun [7], entre otros, han realizado sus simulaciones de prótesis de cadera para obtener resultados equiparables (Tabla 3).

**TABLA 3. Propiedades mecánicas de los materiales seleccionados para realizar los análisis.**

Material	Ti-6Al-4V	T316-L	L-605
Densidad (kg/m <sup>3</sup> )	4500	950	9240
Módulo de Young (GPa)	110	193	240
Módulo de Poisson	0.33	0.3	0.29
Límite elástico (MPa)	920	170	310
Último esfuerzo (GMPa)	950	485	822

### Cargas aplicadas

Para simular las actividades cotidianas que realiza una persona, se aplicaron diferentes cargas estáticas resultantes de las fuerzas generadas por la inercia y los grupos musculares utilizados en cada una de las actividades para una persona de 75 kg (Tabla 4), para lo cual se tomaron como sistema de coordenadas local los ejes x, y, z sobre la cabeza femoral [13].

**TABLA 4. Cargas generadas de las actividades cotidianas (Tomado textualmente de [13]).**

Actividad	Rx (N)	Ry (N)	Rz (N)
Caminar	535.7	-343.5	-1747.2
De pie	575.8	-120.3	-1947.1
Bicicleta	242	-202.5	-651.75
Levantarse	649.8	-203.7	-1428.4
Subir	774.1	-771	-2852.4
Bajar	774.1	-565.7	-1999.6
Sentarse	460.2	-245	-1246.8
Trotar	777.2	-762.7	-2845.2

### RESULTADOS Y DISCUSIÓN

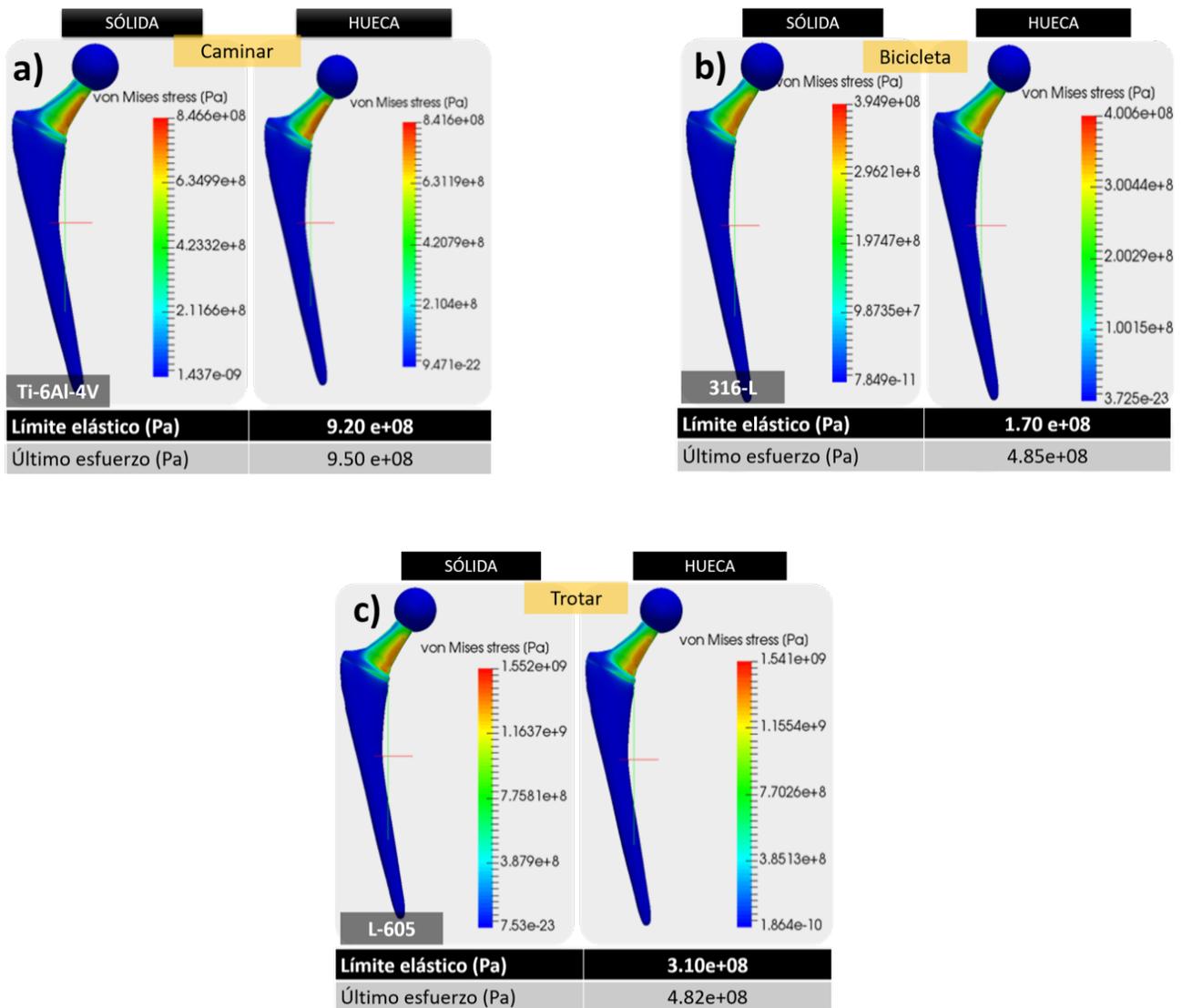
En este proyecto se compararon los resultados de los esfuerzos de von Mises, también conocido como el esfuerzo de máxima energía de distorsión, o Maxwell-Huber-Hencky-Von Mises. Según esta teoría, la cedencia del material comienza cuando la distorsión máxima o la energía de corte en el material es igual a la distorsión máxima o la energía de corte al ceder en una prueba de tensión simple [18]. Se puede demostrar que, para materiales inicialmente elásticos, la energía de deformación o distorsión es proporcional al esfuerzo de von Mises ( $\sigma_{vm}$ ), que es el que se muestra en la ecuación 1.

$$\sigma_{vm} = ((\sigma_1 - \sigma_2)^2 + (\sigma_2 - \sigma_3)^2 + (\sigma_3 - \sigma_1)^2) / 2)^{1/2} \quad (1)$$

Donde  $\sigma_1$ ,  $\sigma_2$ , y  $\sigma_3$  son los esfuerzos principales. El criterio de von Mises alude a que el cuerpo se comporta elásticamente cuando se alcanza la resistencia de cedencia (Ecuación 2):

$$\tau_0 = (3^{1/2}) \sigma_{vm} / 3 \quad (2)$$

Tomando el criterio anterior, comparamos cada valor obtenido del máximo esfuerzo de von Mises de cada material, de cada modelo de prótesis y de cada actividad realizada por el usuario, con respecto al valor del esfuerzo último y el límite elástico (Tabla 3).



**FIGURA 8. Casos tipo: a) Prótesis sin daño estructural, b) Prótesis con deformación permanente, c) Fractura de la prótesis.**

Se sabe que la prótesis sufrirá deformación permanente al rebasar el límite elástico y se fracturará al rebasar el último esfuerzo a la tensión.

Una vez que se realizaron las simulaciones mediante el método de elementos finitos de los 48 casos resultantes, de las combinaciones de cargas debido a las actividades físicas del sujeto objeto de estudio y los materiales propuestos para la prótesis, se obtuvo la distribución de esfuerzos de von Mises sobre los modelos de las prótesis con un código de colores, indicando en color rojo el valor del esfuerzo de von Mises máximo.

Visualmente se puede apreciar que la concentración de esfuerzos se presenta en el cuello de la cabeza femoral, ilustrado en color rojo en la Figura 8c. En completa concordancia con la zona en la que el fémur del paciente sufrió la fractura. Los casos que una prótesis puede tener, derivados de las solicitaciones sobre la misma son: prótesis sin daño estructural, prótesis con deformación permanente y, fractura de la prótesis.

- *Caso a) Prótesis sin daño estructural.* En este caso, la prótesis sólida con el material Ti-6Al-4V, bajo la actividad de caminar presenta un valor del esfuerzo

máximo de von Mises de  $8.466\text{e}+08$  Pa. Mientras que para la prótesis hueca el esfuerzo máximo de von Mises es de  $8.416\text{e}+08$  Pa.

Al comparar dichos valores del esfuerzo máximo de von Mises con el valor reportado en la literatura del esfuerzo en el límite elástico de  $9.20\text{e}+08$  Pa, se logra apreciar que la prótesis tendrá un comportamiento elástico lineal.

De acuerdo con la Ley de Hooke, la prótesis sufrirá deformaciones reversibles una vez que deje tener efecto la carga aplicada. Por otra parte, al tener esfuerzos máximos de von Mises inferiores al último esfuerzo que es de  $9.50\text{e}+08$  Pa, no es posible que sufra fractura alguna (Figura 8a).

- *Caso b) Prótesis con deformación permanente.* En la prótesis de aleación 316-L sometida a las fuerzas derivadas de la acción de andar en bicicleta, se produce un esfuerzo de von Mises  $3.949\text{e}+08$  Pa, para la prótesis sólida. Y un esfuerzo de von Mises  $4.006\text{e}+08$  Pa para la prótesis hueca.

En ambos casos sobrepasan el valor de esfuerzo en el límite elástico que es de  $1.70\text{e}+08$  Pa, por lo que se produce una deformación plástica o permanente en el cuello femoral. Pero que, al no rebasar el último esfuerzo, dicha prótesis no llega a la fractura (Figura 8b).

- *Caso c) Fractura de la prótesis.* En el supuesto caso de que la prótesis diseñada se fabrique de la aleación L-605 y que las fuerzas aplicadas sean el producto de realizar la actividad de trotar. El valor del esfuerzo máximo de von Mises es  $1.552\text{e}+09$  Pa, para la configuración sólida y de  $1.541\text{e}+09$  Pa para la hueca. Dichos valores sobrepasan el valor de esfuerzo en el límite elástico que es de  $3.10\text{e}+08$  Pa, y también el valor del último esfuerzo que para la aleación L-605 es de  $4.82\text{e}+08$  Pa.

Los estados de esfuerzo antes mencionados, producirán una deformación más allá del límite elástico, es decir la cedencia, al alcanzar el esfuerzo último se ocasiona la fractura del material de la prótesis con su consecuente evolución en ruptura (Figura 8c).

Los resultados del esfuerzo máximo de von Mises para las 48 simulaciones en los casos de prótesis hueca y sólida se presentan en la Tabla 5, con sus respectivas condiciones de carga producto de las actividades cotidianas, así como de los materiales de fabricación propuestos.

**TABLA 5. Resultados de los esfuerzos de von Mises.**

Material	Ti-6Al-4V		316-L		L-605	
	Hueco	Sólido	Hueco	Sólido	Hueco	Sólido
Actividad	Esfuerzos von Mises (Pa)					
Caminar	8.42E+08	8.47E+08	8.47E+08	8.57E+08	8.49E+08	8.00E+08
De pie	7.54E+08	7.56E+08	7.62E+08	7.63E+08	7.65E+08	7.66E+08
Bicicleta	3.98E+08	3.90E+08	4.00E+08	3.95E+08	4.02E+08	3.97E+08
Levantarse	6.73E+08	7.03E+08	6.78E+08	7.11E+08	6.79E+08	7.14E+08
Subir	1.56E+09	1.53E+09	1.57E+09	1.55E+09	1.57E+09	1.56E+09
Bajar	1.16E+09	1.14E+09	1.17E+09	1.16E+09	1.17E+09	1.16E+09
Sentarse	6.22E+08	6.29E+08	1.17E+09	8.03E+08	6.27E+08	6.38E+08
Trotar	1.54E+09	1.52E+09	1.55E+09	1.55E+09	1.55E+09	1.54E+09

### Factor de seguridad

Un aspecto importante en el diseño de prótesis es determinar el factor de seguridad (FS). Dicho factor está definido en función del criterio de falla de von Mises, y se muestra en la ecuación 3. El factor de seguridad debe ser mayor o por lo menos igual a uno.

$$FS = \sigma_{lim} / \sigma_{vm} \quad (3)$$

Donde  $\sigma_{lim}$  es el esfuerzo en el límite elástico del material.

Como se puede observar en la Tabla 6, la prótesis hecha de Ti-6Al-4V tiene valores del factor de seguridad superiores a uno.

TABLA 6. Factores de seguridad.

Material	Ti-6Al-4V		316-L		L-605	
	Hueco	Sólido	Hueco	Sólido	Hueco	Sólido
Actividad	Factores de Seguridad					
Caminar	1.09	1.09	0.20	0.20	0.37	0.39
De pie	1.22	1.22	0.22	0.22	0.41	0.40
Bicicleta	2.31	2.36	0.43	0.43	0.77	0.78
Levantarse	1.37	1.31	0.25	0.24	0.46	0.43
Subir	0.59	0.60	0.11	0.11	0.20	0.20
Bajar	0.79	0.81	0.15	0.15	0.27	0.27
Sentarse	1.48	1.46	0.15	0.21	0.49	0.49
Trotar	0.60	0.61	0.11	0.11	0.20	0.20

Lo que significa que resistirá las cargas máximas aplicadas como resultado de realizar las actividades de: Caminar, estar de pie andar en bicicleta, levantarse y sentarse.

TABLA 7. Cargas generadas por un paso completo en marcha humana normal.

Posición	Tiempo (s)	Rx (N)	Ry (N)	Rz (N)
0	0	-119.30	-0.45	-528.30
5	0.059	-181.20	176.94	-1094.00
10	0.118	-245.60	419.22	-1840.00
15	0.177	-282.80	518.40	-2021.00
20	0.236	-273.80	443.25	-1892.00
25	0.295	-247.10	315.99	-1756.00
30	0.354	-223.70	205.29	-1667.00
35	0.413	-186.20	125.64	-1567.00
40	0.413	-142.40	67.14	-1465.00
45	0.472	-71.67	47.48	-1383.00
50	0.531	-21.60	97.47	-1398.00
55	0.59	-143.80	115.20	-1373.00
60	0.649	-355.40	62.82	-1080.00
65	0.708	-322.00	32.27	-801.30
70	0.767	-295.40	7.74	-643.00
75	0.826	-240.20	-9.00	-499.00
80	0.885	-202.10	-16.83	-401.30
85	0.944	-164.00	-503.00	-327.20
90	1.003	-123.20	9.77	-323.60
95	1.121	-100.70	8.69	-437.90
100	1.18	-97.20	-9.00	-509.90

Por otra parte, las actividades como subir y bajar escaleras no las podrá realizar, puesto que comprometen la integridad de la prótesis. Finalmente, se puede decir que las prótesis fabricadas de acero 316-L y L-605 no son recomendables para su uso, puesto que tienen un factor de seguridad inferior a uno.

### Ciclo de marcha

Una prótesis de cadera no recibe cargas constantes, sino que más bien son aleatorias como en el caso del ciclo de marcha, para lo cual se han considerado los datos publicados por [19] [20] [21] y que se muestran en la Tabla 7.

En la Figura 9 se muestra el ciclo de marcha para la prótesis de Ti-6Al-4V. En la cual se pueden apreciar dos picos de esfuerzo de von Mises máximos que concuerdan con los resultados del análisis estático de caminar y de pie. Lo anterior es debido a que para el análisis estático se consideraron las condiciones de máxima carga, y que a los 0.177 segundos de iniciada la marcha se alcanza una condición de máximo esfuerzo, que además resulta ser el máximo absoluto. Por otra parte, el segundo máximo se alcanza a los 1.003 segundos de la marcha, es decir 3 posiciones antes de terminar el ciclo de la marcha.

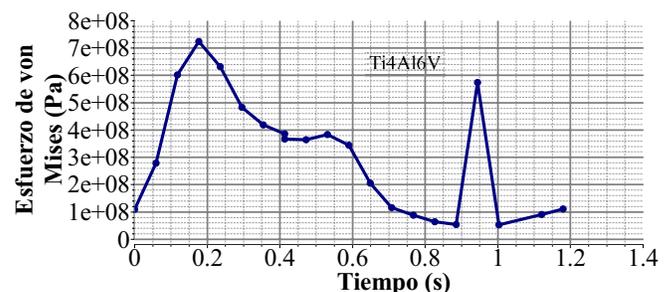


FIGURA 9. Gráfica de esfuerzo de von Mises para el ciclo de marcha con una prótesis de Ti4Al6V.

### Prótesis de Ti-6Al-4V

Para las actividades propuestas a realizar con la prótesis Ti-6Al-4V, podemos observar en la Tabla 5 que, en las condiciones de caminar, parado, andando en bicicleta, levantarse y sentarse, en ambos casos de próte-

sis (prótesis sólida y prótesis hueca), no sufre deformación alguna ni se presentaría riesgo de fractura del cuello femoral. Pero al realizar cualquiera de las actividades como subir escaleras, bajar escaleras y trotar, la prótesis no sólo se deformará permanentemente, sino que se fracturará del cuello femoral, siendo así que de optarse por este modelo el paciente estaría limitado a conservar su peso corporal y a tener restringido la práctica de subir y/o bajar escaleras, así como de trotar.

### **Prótesis de 316-L**

Los modelos de prótesis realizados (sólida y hueca), en todas las actividades sugeridas (Tabla 5), presentan deformación permanente y ruptura del cuello femoral a excepción de andar en bicicleta, ya que al realizar esta actividad la prótesis sufrirá de formación permanente pero no llegará a sufrir fractura. Lo anterior, es debido a que, en una condición ideal, el peso corporal es soportado y distribuido por el asiento de la bicicleta.

### **Prótesis de L-605**

El modelo hueco realizado en este material sufrirá deformación permanente en todas las actividades propuestas, pero únicamente en la condición de caminar, subir y bajar escaleras y trotar la prótesis fallará.

En cuanto al modelo sólido de este mismo material tenemos que la prótesis sufrirá deformación permanente en todas las actividades propuestas, pero a diferencia del modelo hueco solo fallará en tres actividades como la anterior a excepción de caminar (Tabla 5).

## **CONCLUSIONES**

Los resultados obtenidos demuestran que el material idóneo para la fabricación de este tipo de prótesis es el Ti-6Al-4V, además de que éste permitiría realizar modelos tanto sólidos como huecos, suponiendo este último, un ahorro de material y proporcionando mayor ligereza en el modelo.

Cabe mencionar que los resultados son en función del peso del paciente, la topografía que presenta su fémur y las actividades que habitualmente realiza, y que deben de tomarse en cuenta al diseñar la prótesis para una persona con características diferentes y/o con necesidades de actividad física diferente, lo que hace necesario robustecer el cuello femoral ya que es el punto donde la prótesis tiende a fallar.

Finalmente, y como resultado del factor de seguridad para las diversas actividades, se propone mejorar el diseño a nivel del cuello femoral para así obtener un factor de seguridad superior a uno y garantizar la durabilidad y funcionalidad de la prótesis.

## **CONTRIBUCIÓN DE LOS AUTORES**

K. H. R. y M. V. G. realizaron el modelado y las simulaciones; K. H. R. elaboró gráficas y tablas; A. B. M. V. llevó a cabo el análisis estructural, revisión y corrección de estilo; A. B. M. V. y L. B. G. asesoría en materias; M. V. G. segmentó las imágenes médicas, análisis biomecánico, diseño y estructura, revisión de modelos computacionales.

## REFERENCIAS

- [1] Charnley J, Cupic Z. The nine and ten year results of the low-friction arthroplasty of the hip. *Clin Orthop Relat Res.* 1973;95:9-25.
- [2] Griza S, Kwietniewski C, Tarnowski GA, Bertoni F, Reboh Y, Strohaecker TR, et al. Fatigue failure analysis of a specific total hip prosthesis stem design. *Int J Fatigue.* 2008;30:1325-32. <https://doi.org/10.1016/j.ijfatigue.2007.11.005>
- [3] Hedia HS, Barton DC, Fisher J, Elmidany TT. A method for shape optimization of a hip prosthesis to maximize the fatigue life of the cement. *Med Eng Phys.* 1996;18:647-54. [https://doi.org/10.1016/S1350-4533\(96\)00025-2](https://doi.org/10.1016/S1350-4533(96)00025-2)
- [4] Baxmann M, Pfaff AM, Schilling C, Grupp TM, Morlock MM. Biomechanical Evaluation of the Fatigue Performance, the Taper Corrosion and the Metal Ion Release of a Dual Taper Hip Prosthesis under Physiological Environmental Conditions. *Biotribology.* 2017;12:1-7. <https://doi.org/10.1016/j.biotri.2017.07.002>
- [5] Lanzutti A, Andreatta F, Rossi L, Di Benedetto P, Causero A, Magnan M, et al. Corrosion fatigue failure of a high carbon CoCrMo modular hip prosthesis: Failure analysis and electrochemical study. *Eng Fail Anal.* 2019;105:856-68. <https://doi.org/10.1016/j.engfailanal.2019.07.044>
- [6] Gross S, Abel EW. A finite element analysis of hollow stemmed hip prostheses as a means of reducing stress shielding of the femur. *J Biomech.* 2001;34:995-1003. [https://doi.org/10.1016/S0021-9290\(01\)00072-0](https://doi.org/10.1016/S0021-9290(01)00072-0)
- [7] Sun C, Wang L, Kang J, Li D, Jin Z. Biomechanical Optimization of Elastic Modulus Distribution in Porous Femoral Stem for Artificial Hip Joints. *J Bionic Eng.* 2018;15:693-702. <https://doi.org/10.1007/s42235-018-0057-1>
- [8] Yan W, Berthe J, Wen C. Numerical investigation of the effect of porous titanium femoral prosthesis on bone remodeling. *Mater Des.* 2011;32:1776-82. <https://doi.org/10.1016/j.matdes.2010.12.042>
- [9] Martel O, Afonso H, Bermejo J, Cuadrado A, Monopoli D. Análisis comparativo de prótesis de cadera: implantes tradicionales frente a implantes mínimamente invasivos. *Rev Iberoam Ing mecánica.* 2011;15:85-94.
- [10] Domínguez-Hernández VM, Carbajal Romero MF, Rico Martínez G, Urriolaigoitia Calderón G. Análisis de una prótesis no convencional bloqueada para cadera mediante el método del elemento finito. *Rev Mex Ing Biomédica.* 2003; 24(1): 37-44.
- [11] Bae JY, Farooque U, Lee KW, Kim GH, Jeon I, Yoon TR. Development of hip joint prostheses with modular stems. *CAD Comput Aided Des.* 2011;43:1173-80. <https://doi.org/10.1016/j.cad.2011.05.004>
- [12] Niemczewska-Wójcik M. The influence of the surface geometric structure on the functionality of implants. *Wear.* 2011;271:596-603. <https://doi.org/10.1016/j.wear.2010.06.013>
- [13] Canci P. FE Parametric Model (Patient Specific) of a Femur [master's thesis]. [Milano]:Politecnico di Milano; 2015. 97p. Italian.
- [14] Mahiques Oltra A. Estudio de diseño y cálculo de una prótesis de cadera [dissertation]. [Valencia]: Universitat Politècnica de València, 2015. 141p. Spanish.
- [15] Arellano Guerrero RE. Análisis estático de prótesis de cadera tipo Spotorno® mediante F.E.M. [dissertation]. [Ciudad de México]: Universidad Nacional Autónoma de México, 2015. 64p. Spanish.
- [16] Hazlehurst KB. The adoption of laser melting technology for the manufacture of functionally graded cobalt chrome alloy femoral stems [Ph.D.'s thesis]. [Wolverhampton]:University of Wolverhampton, 2014.167p.
- [17] Losa Zapico P. Diseño de una prótesis liviana de cadera con la posibilidad de incorporar medicación[dissertation]. [Madrid]: Universidad Politécnica de Madrid, 2018. 154p. Spanish.
- [18] Helena HJ. Theory of elasticity and plasticity. 1a ed. Delhi: PHI Learning Private Limited.; 2017. 264 p.
- [19] Delgado Rosas M, Enriquez Espino J. Distribución de esfuerzos en una prótesis parcial de cadera cementada. *Ing Mecánica Tecnol y Desarro* 2005;2:1-5.
- [20] Heller MO, Bergmann G, Kassi J-P, Claes L, Haas NP, Duda GN. Determination of muscle loading at the hip joint for use in pre-clinical testing. *J Biomech* 2005;38:1155-63. <https://doi.org/https://doi.org/10.1016/j.jbiomech.2004.05.022>
- [21] Martínez Delfín A, García de la Figal Costales J, Rodríguez Milián LM, Rodríguez Pérez R. Fatigue behavior stem hip prosthesis for walking. *Rev Ing Mecánica.* 2014;17:1-11.

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## Determination of maximum noise level in an ECG channel under SURE Wavelet filtering for HRV extraction

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### ABSTRACT

Heart Rate Variability (HRV) is the measure of variation between R-R interbeats, it has been demonstrated to be a good representation of physiological features, especially to the alterations in the Autonomic Nervous System (ANS). Considering the values that compose a HRV distribution are extracted from electrocardiography (ECG), many of the electrical disturbances that affect ECG-based diagnosis can also interfere with the results of the HRV analysis. This paper uses a 30-minute portion of a healthy patient (no arrhythmias detected or annotated) from the MIT-BIH ECG database to analyze the effectiveness of the SURE Wavelet denoising method for extracting the HRV from a progressively noisier ECG channel. Results show that the minimum SNR for reliable HRV extraction under these conditions is approximately 5dB and outlines the exponential behavior of HRV extraction for escalating noise levels in the ECG signal.

**KEYWORDS:** HRV; ECG filtering; SNR; Wavelet.

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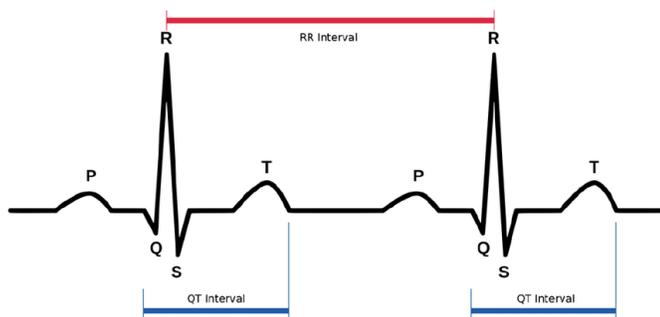
## INTRODUCTION

Heart Rate Variability (HRV) is currently the most common digital application of analysis of the ECG signal trace. It refers to a precise time measurement (usually in the order of milliseconds) of the intervals between each heartbeat, represented in Figure 1, labeled as R-R interval [1].

The object of interest when analyzing variations in heart rate is autonomic nervous system (ANS), which is a division of the peripheral nervous system that acts in the regulation of bodily functions such as heart rate, respiratory rate and digestion [2].

It is largely regarded as the primary control mechanism of the fight-or-flight reaction (or hyper-arousal) [3].

In the past few decades, researchers have discovered correlation of the HRV analysis with many different health related issues, ranging from the autonomic function of insulin-dependent diabetic patients [4] to the aftereffects of myocardial infarction [5].



**FIGURE 1.** A pair of heartbeat cycles as observed by the electrocardiograph, indicating the major 4 points of reference in electrocardiographic analysis: the T and P waves, as well as the QRS complex. The period between two R-peaks is also represented in the picture and is of great importance for HRV acquisition [6].

The most usual method of extracting HRV data is the detection of R-wave peaks in an ECG trace plot. Therefore, when dealing with acquired signals, the

HRV can be compromised by the occurrence of artifacts originated by electrode motion, respiration motion (baseline wander) or even irradiated electromagnetic noise [7]. Considering that the relevant information to the HRV analysis is the reliable detection of the R peak, the design of filtering methods for this purpose is slightly different from the popular methods used for ECG filtering [8].

The signal to noise ratio (SNR) is a dimensionless ratio comparing the signal and noise power in a given channel [9].

$$SNR(\text{dB}) = 10 * \log \left( \frac{P_s}{P_N} \right) \quad (1)$$

This ratio is described in Equation 1 in its most usual form, where  $P_s$  stands for the power of the signal being analyzed and  $P_N$  stands for the power of the noise source. The result is displayed in decibels (dB) [10].

The electrical engineering academic consensus is that 3dB in signal-to-noise ratio is the minimum value for the system to be considered acceptable in terms of the fidelity of signal output [11]. This threshold was obtained using Equation 1.

$$F(a, b) = \int_0^{\infty} f(x) \psi_{(a,b)}^*(x) dx \quad (2)$$

The Wavelet Transform is represented in its most general form in Equation 2 for a given function  $f(x)$ , having  $\psi$  as a continuous function for the mother Wavelet, accepting two parameters:  $a$  for scaling and  $b$  as the translational value. It can be used as a denoising method and is especially useful dealing with sharp transients in the signal.

Different methods using Wavelet have been developed over the years. Wavelet Shrinkage provides a great filter with low computational power [12]. Some other well-known Wavelets denoising methods are known as Bayes, BlockJS, Minimax, SURE and

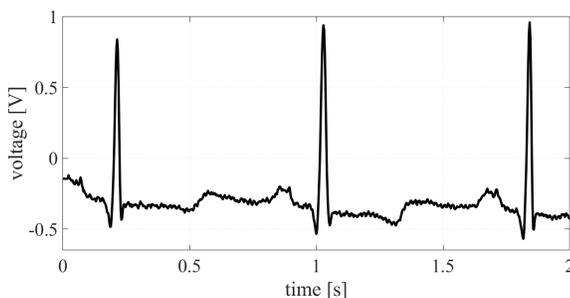
Universal Threshold [13], all of which have been gaining on popularity since being incorporated into programming libraries on different platforms such as MATLAB and Python.

This paper proposes to analyze the process of extracting the HRV from a progressively noisier ECG channel in order to find out what is the minimum SNR with which SURE Wavelet denoising is still sufficient. The aim is to determine the limitation of this method of filtering specifically for HRV analysis.

### MATERIALS AND METHODS

The ECG signal used for the HRV analysis was obtained from the MIT-BIH Arrhythmia ECG database [14]. This database was selected due to the long monitoring duration of each single patient (6-hour periods) available, enabling the collection of a sizeable sample of R-R intervals. From the records available, a 30-minute ECG record from a healthy patient (i.e. without observed arrhythmias) was chosen.

A short sample of the signal used is represented in Figure 2. It is important to consider that this signal has not yet went through the R-R identifying algorithm.

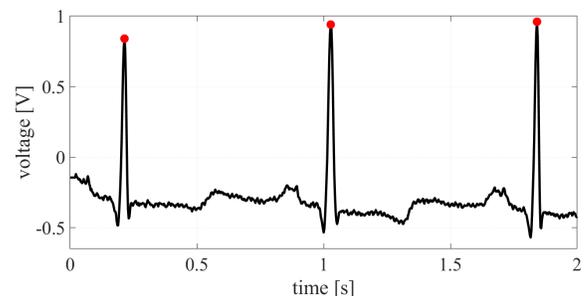


**FIGURE 2. Sample of electrocardiographic signal acquired from the MIT-BIH Arrhythmia Database [15].**

Application of filtering methods and general signal preprocessing were made through the software Mathworks MATLAB 2016b with the custom library BioSigKit V1.0 [16] which was used for the extraction of the R-peaks through the Pan-Tompkins algorithm.

Signal was sampled at 360 Hz and filtered with the SURE Wavelet Transform as a denoising method with 5 levels of decomposition. This particular method of denoising was chosen because of its availability in most Wavelet toolboxes, its low demand in processing power and its good performance for biophysiological signal processing (especially for ECG and EEG applications) [17].

The R-peak detection algorithm (specifically the Pan-Tompkins implementation [16]) is implemented onto the signal represented in Figure 3 after it is filtered.



**FIGURE 3. The same portion of the database represented in Figure 2 after the implementation of the Pan-Tompkins algorithm. Location of the R-peaks are marked with a red dot.**

Points marked with red in Figure 3 were used to create the HRV vector. The process is a simple subtraction between the time values associated with two consecutive R-peak points, repeating the process all along the record.

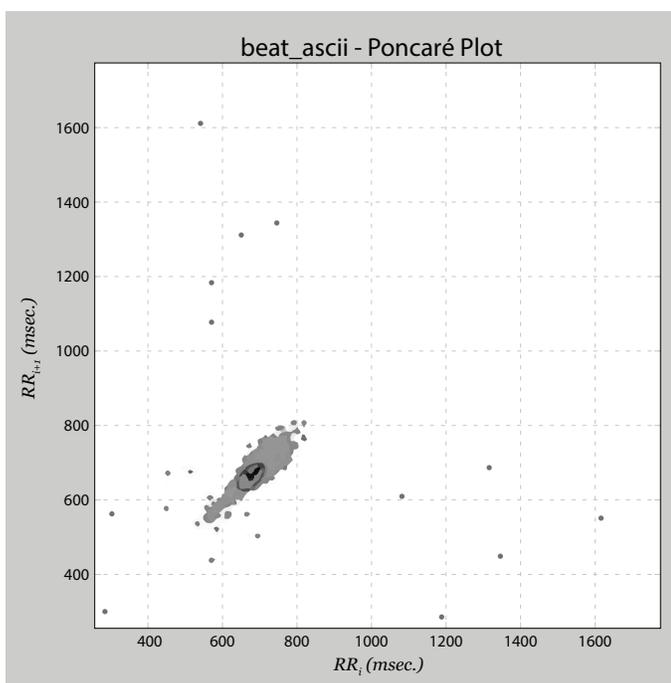
This is done once in order to obtain the real mean HRV (which consists of an arithmetic mean of all of the R-R values contained in the HRV vector) observed in the original 30-minute ECG record. The ECG signal is then summed with a matrix with random noise, this process is repeated in order to generate an ECG matrix with escalating noise level (each time noise power is incremented by 0.1).

Every newly generated noisy signal then undergoes the same SURE Wavelet method of denoising presented before, which in turns created the final matrix.

From this final matrix, HRV is then extracted, also it is labeled with its SNR level using Equation 1 which will reflect the white noise added to it. This whole process is repeated 21 times, creating the matrixes in different noise-levels that will be needed for the analysis.

A possible way to represent HRV extracted from the progressively noisier channel is utilizing a Poincaré plot [18]. Which is a recursive plot since its axis represent a current measurement (called  $RR(n)$ ) and a future measurement ( $RR(n+1)$ ) repeated for many instances [18]. In a completely stable phenomenon, all points of the plot should be grouped together as tight as possible. When the subject is the human heart, that doesn't always happen for different reasons.

If the Poincaré in Figure 4 were data gathered from one subjects heart-rate variability, points observed in the extremities of the plot could either be the representation of some kind of intermittent cardiac function abnormality or the malfunctioning of the R-peak detection algorithm induced by noise in the signal.

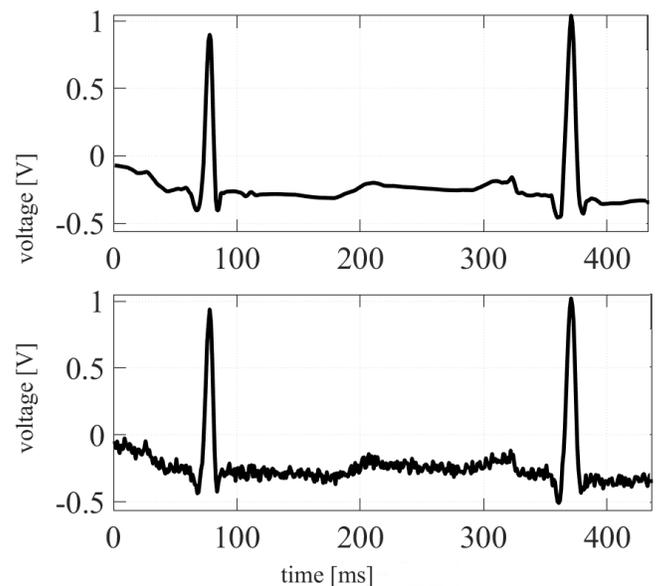


**FIGURE 4.** Example of a Poincaré being used to find outlier points in a determinate process [18].

The correlation between mean HRV and the SNR observed in the ECG channel (after the noise adding and SURE Wavelet denoising process described) reveals the point in the curve where the level of noise is not compatible with the HRV extraction (i.e. the point where the values being extracted are not representative of the signals coming from the patient's body, but are mostly caused by the noisy ECG).

## RESULTS AND DISCUSSION

The chosen portion of the signal is filtered through the SURE Wavelet denoising tool and a small part of is represented in Figure 5.



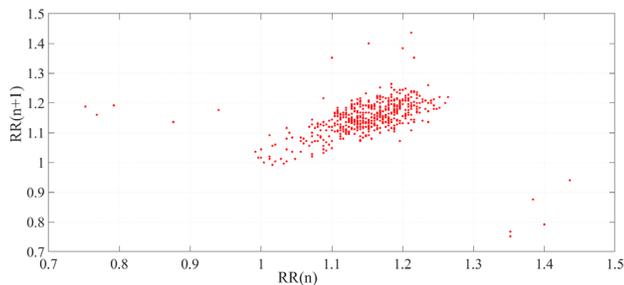
**FIGURE 5.** Below: Regular electrocardiographic signal (as extracted from the database). Above: the same portion of the signal filtered with the SURE Wavelet denoising method for 5 levels of decomposition.

The Pan-Tompkins R-peak detection algorithm shown in Figure 3 is implemented on the filtered signal in order to extract the locations of every R-peak detected throughout the recording.

A Poincaré plot is used to represent the extracted HRV distribution in Figure 6. It useful here because it makes possible the visual analysis of increasing noise.

As expected from a filtered low-noise channel, the higher density of points in the center of the plot is visually recognizable.

Such artifacts are expected as HRV analysis usually focuses more on the total distribution of the plot and less on the outlier points [19].



**FIGURE 6. HRV Poincaré plot extracted from electrocardiographic signal from the database before random noise is added, filtered through SURE Wavelet.**

White noise is added to the original database electrocardiographic signal and is then filtered with the aforementioned Wavelet method. This process is repeated 21 times, increasing the white noise power linearly in each iteration by a factor of 0.1.

The R-peak detection and HRV analysis are repeated for each iteration, calculating the mean HRV value for each new noise-contaminated ECG signals.

All of the signals are shown in Table I. The first one, of infinite SNR, represents the original signal, without white noise being added to it. The subsequent signals represent every increase in white-noise power added to the original signal.

Considering that the first measurement is made without adding noise to our channel, the correct mean HRV for the 30-minute recording is 52.385ms. Therefore, any alteration in the calculated mean HRV can be interpreted as an error introduced by the random noise added to the original ECG signal.

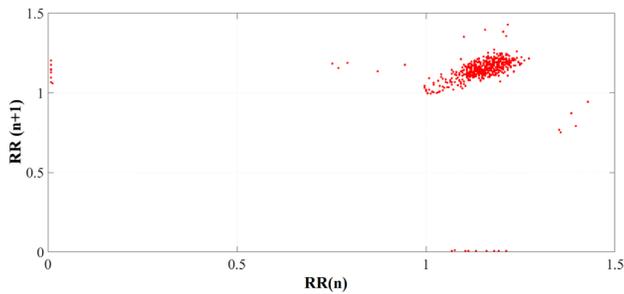
**TABLE 1. Simulated SNR (dB) and Mean HRV (ms) values.**

Calculated SNR (dB)	Mean HRV (ms)
$\infty$	52.385
21.949	52.385
21.949	52.385
15.923	52.384
12.402	52.385
9.909	52.386
7.981	52.385
6.385	52.384
5.050	52.384
3.894	66.384
2.858	80.867
1.940	80.867
1.127	109.131
0.366	179.036
-0.320	206.385
-0.970	274.298
-1.560	327.727
-2.113	283.082
-2.657	508.656
-3.166	504.919
-3.628	445.768
-4.061	627.981

Calculated values are consistent with prior knowledge about SNR considerations in signal transmission quality. Alterations on the calculated mean HRV can be observed after the signal-to-noise ratio drops below 5 dB.

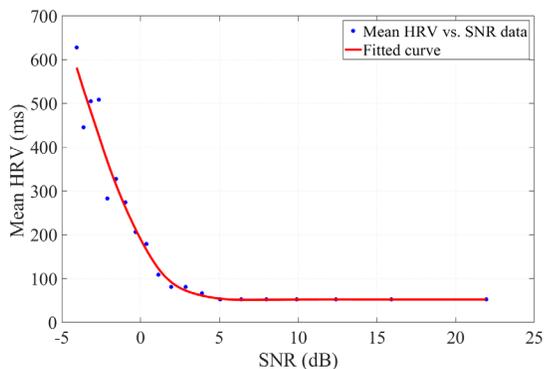
The effects of the noisy ECG can be observed in the Poincaré plot of the HRV as represented in Figure 6. The scattered points are more frequent and can be found further away from the centroids location.

In this case, calculated mean HRV is 274.298ms which is not a physiologically meaningful value, since it exceeds even the highest possible expected heart rate variation.



**FIGURE 7. HRV Poincaré plot extracted from ECG signal with SNR equal to -0.970. A high concentration of points in the extremities of the plot indicate that the channel with this noise-level may be unsuitable for HRV analysis.**

Experimental values as described in Table I are represented graphically in Figure 7 and a trend curve is fitted using the Smoothing Spline method.



**FIGURE 8. Relationship between SNR and Mean HRV.**

The graph shows the mostly linear behavior of the HRV calculation algorithm applied to the filtered channel when SNR is higher than 5dB and the exponential behavior of the mean HRV calculation when noise component increases.

## CONCLUSIONS

This paper has demonstrated the limitations of one of the more common filtering techniques applied to ECG channels for this particular HRV distribution. Results suggests that a standard Wavelet denoising method (in this case SURE method with 5 levels of

decomposition) looks to be insufficient to ensure reliable HRV extraction when SNR is under that of approximately 5 Db. In order for it to be confirmed a study using many different databases has to be done in the future.

These findings could be important both to research and to industries that work on health-monitoring wearable devices, since we were able to define with precision the level of noise in which HRV reading will stop being reliable.

Future research in this area should focus on the development of a filtering method specific to HRV analysis in order to better preserve nominal values of mean HRV calculated from noisy ECG signals and of course, extend this study to include many more different databases.

## Ethical statement

The authors declare that there is no conflict of interest regarding the publication of this article

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## AUTHOR CONTRIBUTIONS

R.N.C. conceived and designed the work, he participated in the data acquisition, initial analyses, data interpretation and first drafting of the writing. P.B.F. Contributed substantially to the manuscript, reviewed and approved the final version, reviewed all aspects of the work, ensuring that questions related to the accuracy or integrity of the project were appropriately investigated and resolved. Both authors have equally contributed to the work in each stage of its development.

## REFERENCES

- [1] Mendis S, Puska P, Norrving B. Global atlas on cardiovascular disease prevention and control [Internet]. Geneva: World Health Organization; 2011. Available from: [https://www.who.int/cardiovascular\\_diseases/publications/atlas\\_cvd/en/](https://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/)
- [2] Hall JE. Guyton and Hall textbook of medical physiology e-Book. 12th edition. Philadelphia: Elsevier Health Sciences; 2010.
- [3] Bayés De Luna A. Basic electrocardiography: normal and abnormal ECG patterns. Hershey, PA: John Wiley & Sons; 2008. <https://doi.org/10.1002/9780470692622.ch4>
- [4] Freeman R, Saul JP, Roberts MS, Berger RD, Broadbridge C, Cohen RJ. Spectral analysis of heart rate in diabetic autonomic neuropathy: a comparison with standard tests of autonomic function. Archives of Neurology. 1991;48(2):185-90. <https://doi.org/10.1001/archneur.1991.00530140079020>
- [5] Rothschild M, Rothschild A, Pfeifer M. Temporary decrease in cardiac parasympathetic tone after acute myocardial infarction. The American journal of cardiology. 1988;62(9):637-9. [https://doi.org/10.1016/0002-9149\(88\)90670-4](https://doi.org/10.1016/0002-9149(88)90670-4)
- [6] Page A, Hassanaliheragh M, Soyata T, Aktas MK, Kantarci B, Andrescu S. Conceptualizing a real-time remote cardiac health monitoring system. In Medical Imaging: Concepts, Methodologies, Tools, and Applications. Hershey, PA: IGI Global; 2017. p.160-193. <https://doi.org/10.4018/978-1-4666-8662-5.CH001>
- [7] Joshi SL, Vatti RA, Tornekar RV. A survey on ECG signal denoising techniques. 2013 International Conference on Communication Systems and Network Technologies. Gwalior, India: IEEE; 2013. p. 60-64. <https://doi.org/10.1109/CSNT.2013.22>
- [8] Zhang D. Wavelet approach for ECG baseline wander correction and noise reduction. 2005 IEEE Engineering in Medicine and Biology 27th Annual Conference. Shanghai: IEEE; 2005. p. 1212-1215. <https://doi.org/10.1109/IEMBS.2005.1616642>
- [9] Allisy-Roberts PJ, Williams J. Farr's physics for medical imaging. 2nd edition. Europe: Saunders- Elsevier; 2008.
- [10] Sijbers J, Scheunders P, Bonnet N, Van Dyck D, Raman E. Quantification and improvement of the signal-to-noise ratio in a magnetic resonance image acquisition procedure. Magnetic resonance imaging. 1996;14(10):1157-63. [https://doi.org/10.1016/S0730-725X\(96\)00219-6](https://doi.org/10.1016/S0730-725X(96)00219-6)
- [11] Johnson DH. Signal-to-noise ratio. Scholarpedia [Internet]. 2006;1(12): 2088. Available from: [http://www.scholarpedia.org/article/Signal-to-noise\\_ratio](http://www.scholarpedia.org/article/Signal-to-noise_ratio)
- [12] Srivastava M, Anderson CL, Freed JH. A New Wavelet Denoising Method for Selecting Decomposition Levels and Noise Thresholds. IEEE Access. 2016;4:3862-77. <https://doi.org/10.1109/ACCESS.2016.2587581>
- [13] Antoniadis A. Wavelets in statistics: a review. Journal of the Italian Statistical Society. 1997; 6: 97. <https://doi.org/10.1007/BF03178905>
- [14] Goldberger AL, Amaral LA, Glass L, Hausdorff JM, Ivanov PC, Mark, Mietus JE, Moody GB, Peng CK, Stanley HE. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation. 2000;101(23): E215-E220. <https://doi.org/10.1161/01.cir.101.23.e215>
- [15] Moody GB, Mark RG. The MIT-BIH arrhythmia database on CD-ROM and software for use with it. Proceedings Computers in Cardiology. Chicago: IEEE; 1990. p. 185-188. <https://doi.org/10.1109/CIC.1990.144205>
- [16] Sedghamiz H. BioSigKit: A Matlab Toolbox and Interface for Analysis of BioSignals. Journal of Open Source Software. 2018;3(30): 671. <https://doi.org/10.21105/joss.00671>
- [17] Geetha G, Geethalakshmi SN. EEG De-noising using SURE Thresholding based on Wavelet Transforms. International Journal of Computer Applications. 2011;24(6):29-33. <https://doi.org/10.5120/2948-3935>
- [18] Rodríguez-Liñares L, Lado MJ, Vila XA, Méndez AJ, Cuesta P. gHRV: Heart rate variability analysis made easy. Computer methods and programs in biomedicine. 2014;116(1):26-38. <https://doi.org/10.1016/j.cmpb.2014.04.007>
- [19] Hsu CH, Tsai MY, Huang GS, Lin TC, Chen KP, Ho ST, Shyu LY, Li CY. Poincaré plot indexes of heart rate variability detect dynamic autonomic modulation during general anesthesia induction. Acta Anaesthesiologica Taiwanica. 2012;50(1):12-8. <https://doi.org/10.1016/j.aat.2012.03.002>